ROLE OF SERUM URIC ACID AS A BIOMARKER IN HEART FAILURE

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CERTIFICATE

This is to certify that the dissertation entitled "**ROLE OF SERUM URIC ACID AS A BIOMARKER IN HEART FAILURE"** is a bonafide work done by **Dr.VIJAYSHREE.G.**, at Madras Medical College, Chennai in partial fulfillment of the university rules and regulations for award of M.D., Degree in General Medicine (Branch-I) under my guidance and supervision during the academic year 2009 -2012.

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DECLARATION

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TABLE OF CONTENTS

ABBREVIATIONS

ACC/AHA	American college of cardiology/American heart association
ANOVA	One-way Analysis of Variance
ATP	Adenosine Tri Phosphate
ATT	Anti tuberculous therapy
AV	Atrio ventricular
BNP	Brain Natriuretic Peptide
CAD	Coronary artery disease
CHF	Chronic heart failure
COPD	Chronic obstructive pulmonary disease
CV	Cardiovascular
DCM	Dilated cardiomyopathy
DNA	Deoxy ribonucleic acid
ECG	Electrocardiogram
EDV	End diastolic volume
EF	Ejection fraction
GFR	Glomerular filtration rate
HDL	High density lipoprotein
HF	Heart failure
KG	Kilogram
LDL	Low density lipoprotein
LV	Left Ventricle
MI	Myocardial infarction
NO	Nitric oxide
NYHA	Newyork Heart Association

RAA	Renin-angiotensin-aldosterone
RHD	Rheumatic heart disease
RNA	Ribo nucleic acid
ROS	Reactive Oxygen species
RT	Room temperature
SUA	Serum uric acid
SV	Stroke volume
TNF	Tumour Necrosis Factor
UA	Uric acid
XO	Xanthine oxidase

INTRODUCTION

It is universally accepted that Heart Failure is a complex clinical syndrome that can result from any structural or functional cardiac disorders that impairs the ability of ventricles to fill with or eject blood. Coronary artery disease accounts for a substantial portion of patients with chronic Heart failure. Heart failure is the end stage of all diseases of the heart and is a major cause of morbidity and mortality [1].

Heart failure is a burgeoning problem worldwide. The prevalence of heart failure increases with age[1].

Heart failure is associated with elevations in circulating levels of Brain Natriuretic Peptide (BNP) and other markers like Uric acid, Troponin T and I, C- Reactive Protein, TNF Receptors, E- Selectin etc.

As Heart failure is a leading cause of mortality, the ability to predict prognosis is essential for optimal allocation of treatments. Biomarkers offering prognostic information are used in practice. Studies have shown that apart from Brain Natriuretic Peptide as a biomarker, Uric acid is found to have prognostic value as well[2].

Increased Serum Uric acid in cardiovascular events may be a consequence of impairment of vascular Nitric Oxide, owing to the ability of

Nitric Oxide to modulate Uric acid through its influence on Xanthine Oxidase. Activation of Xanthine Oxidase through free radical release causes leucocyte and endothelial cell activation[3]. Increases in Uric acid are associated with increased vascular tone and depressed myocardial contractility via increase in Xanthine Oxidase activity. Thus Uric acid could be associated with haemodynamic compromise in heart failure.

Tamariz et al. in a metaanalysis in 2011 analyzed 1456 patients with Heart failure. Relative risk of all-cause mortality was found to be 2.13 for those with serum Uric acid > 6.5 mg/dl compared with uric acid < 6.5 mg/dl. A linear association was found between serum uric acid levels and mortality after 7 mg/dl[4].

Other Studies have shown that Uric acid is a strong independent marker of worser prognosis in patients with moderate to severe Congestive Heart Failure. In patients with heart failure, increased levels of serum Uric acid are highly predictive of mortality and are useful in identifying the need for Heart transplantation.

Hence Uric acid is valuable as a biomarker in patients with Heart Failure.

AIM OF THE STUDY

- To evaluate serum uric acid levels in patients with heart failure.
- To correlate serum uric acid levels with morbidity and mortality in patients with heart failure.
- To correlate serum uric acid levels with prognosis in heart failure.

REVIEW OF LITERATURE

HISTORICAL REVIEW

Descriptions of heart failure exist from ancient Egypt, Greece, and India. Little understanding of the nature of the condition can have existed until William Harvey described the circulation in 1628[53].

Roentgen's discovery of X rays and Einthoven's development of electrocardiography in the 1890s led to improvements in the investigation of heart failure. The advent of echocardiography, cardiac catheterisation, and nuclear medicine have improved the investigation and diagnosis of patients with heart failure.

It was not until the 20th century that diuretics were developed. The early, mercurial agents, however, were associated with substantial toxicity, unlike the thiazide diuretics, which were introduced in the 1950s. Vasodilators were not widely used until the development of angiotensin converting enzyme inhibitors in the 1970s. The landmark CONSENSUS-I study (first cooperative north Scandinavian enalapril survival study), published in 1987, showed the unequivocal survival benefits of enalapril in patients with severe heart failure.

The therapy for heart failure has emerged from the use of diuretics and vasodilators to the use of implantable Cardioverter-Defibrillators, Ventricular Assist devices, LV reconstruction procedures, Cardiac resynchronisation therapy and Cardiac transplantation[53].

EPIDEMIOLOGY OF HEART FAILURE

Heart failure is a burgeoning problem worldwide, with more than 20 million people affected. The overall prevalence of HF in the adult population in developed countries is 2%[1].

Heart failure prevalence follows an exponential pattern, rising with age, and affects 6–10% of people over age 65. Although the relative incidence of HF is lower in women than in men, women constitute at least one-half of the cases of HF because of their longer life expectancy[1]. In North America and Europe, the lifetime risk of developing HF is approximately one in five for a 40-year-old.

The overall prevalence of HF is thought to be increasing, in part because current therapies for cardiac disorders, such as myocardial infarction (MI), valvular heart disease, and arrhythmias, are allowing patients to survive longer. Very little is known about the prevalence or risk of developing HF in

emerging nations because of the lack of population-based studies in these countries.

Based on disease-specific estimates of prevalence and incidence rates of heart failure, it has been estimated that the prevalence of heart failure in India due to coronary heart disease, hypertension, obesity, diabetes and rheumatic heart disease ranges from 1.3 to 4.6 million, with an annual incidence of around 1.8 million[54].

Although HF once was thought to arise primarily in the setting of a depressed left ventricular (LV) ejection fraction (EF), epidemiologic studies have shown that approximately one-half of patients who develop HF have a normal or preserved EF (EF 40–50%). Accordingly, HF patients are now broadly categorized into one of two groups: (1) HF with a depressed EF (commonly referred to as *systolic failure*) or (2) HF with a preserved EF (commonly referred to as *diastolic failure*) [1].

Any condition that leads to an alteration in LV structure or function can predispose a patient to developing HF. Although the etiology of HF in patients with a preserved EF differs from that of patients with depressed EF, there is considerable overlap between the etiologies of these two conditions.

In industrialized countries, coronary artery disease (CAD) has become the predominant cause in men and women and is responsible for 60–75% of cases of HF. Hypertension contributes to the development of HF in 75% of patients, including most patients with CAD. Both CAD and hypertension interact to augment the risk of HF, as does diabetes mellitus.

DEFINITION OF HEART FAILURE

The most accepted and practical definition of heart failure appeared in 2001 ACC/AHA guidelines for the evaluation and management of heart failure in adults which states ''Heart Failure is a complex clinical syndrome that can result from any structural or functional cardiac disorders that impairs the ability of ventricles to fill with or eject blood''[53].

ETIOLOGY OF HEART FAILURE

Depressed Ejection Fraction (<40%)	
Coronary artery disease	Nonischemic dilated cardiomyopathy
Myocardial infarction	Familial/genetic disorders
Myocardial ischemia	Infiltrative disorders
Chronic pressure overload	Toxic/drug-induced damage
Hypertension	Metabolic disorder
Obstructive valvular disease	Viral
Chronic volume overload	Chagas' disease
Regurgitant valvular disease	Disorders of rate and rhythm
Intracardiac (left-to-right) shunting	Chronic bradyarrhythmias
Extracardiac shunting	Chronic tachyarrhythmias
Preserved Ejection Fraction (>40–50%)	
Pathologic hypertrophy	Restrictive cardiomyopathy
Primary(hypertrophic cardiomyopathies)	Infiltrative disorders (amyloidosis, sarcoidosis)
Secondary (hypertension)	Storage diseases (hemochromatosis)
Aging	Fibrosis
	Endomyocardial disorders
Pulmonary Heart Disease	
Cor pulmonale	
Pulmonary vascular disorders	
High-Output States	
Metabolic disorders	Excessive blood-flow requirements
Thyrotoxicosis	Systemic arteriovenous shunting
Nutritional disorders (beriberi)	Chronic anemia

In 20–30% of the cases of HF with a depressed EF, the exact etiologic basis is not known. These patients are referred to as having nonischemic, dilated, or idiopathic cardiomyopathy if the cause is unknown. Prior viral infection or toxin exposure (e.g., alcoholic or chemotherapeutic) also may lead to a dilated cardiomyopathy[1].

Moreover, it is becoming increasingly clear that a large number of cases of dilated cardiomyopathy are secondary to specific genetic defects, most notably those in the cytoskeleton. Most forms of familial dilated cardiomyopathy are inherited in an autosomal dominant fashion. Mutations of genes that encode cytoskeletal proteins (desmin, cardiac myosin, vinculin) and nuclear membrane proteins (laminin) have been identified thus far.

Dilated cardiomyopathy also is associated with Duchenne's, Becker's, and limb-girdle muscular dystrophies. Conditions that lead to a high cardiac output (e.g., arteriovenous fistula, anemia) are seldom responsible for the development of HF in a normal heart; however, in the presence of underlying structural heart disease, these conditions can lead to overt HF[1].

PATHOGENESIS OF HEART FAILURE

Heart failure syndrome always begins with an index event. The index or the initiating event may be clinically silent, such as the expression of a

genetic mutation, or obvious, such as the catastrophic, sudden loss of a large mass of contractile tissue from acute myocardial infarction.

The index event could be the explosive onset of fulminant viral myocarditis, or it may be prolonged and insidious, such as that occurs with valvular heart disease. The phenotypic expression of left ventricle dilation and impaired systolic function can also be slow to develop, such as a pressure or volume overloaded state from valvular or coronary heart disease. The clinical picture can also be more rapidly progressive, as sometimes occurs with familial cardiomyopathy.

In most instances, patients remain asymptomatic or minimally symptomatic after the initial decline in pumping capacity of the heart or develop symptoms only after the dysfunction has been present for some time.

The list of compensatory mechanisms that have been described thus far include (1) activation of the renin-angiotensin-aldosterone (RAA) and adrenergic nervous systems, which are responsible for maintaining cardiac output through increased retention of salt and water, and (2) increased myocardial contractility. In addition, there is activation of a family of countervailing vasodilatory molecules, including the atrial and brain natriuretic

peptides (ANP and BNP), prostaglandins (PGE2 and PGI2), and nitric oxide (NO), that offsets the excessive peripheral vascular vasoconstriction.

Although the exact mechanisms that are responsible for this transition are not known, the transition to symptomatic HF is accompanied by increasing activation of neurohormonal, adrenergic, and cytokine systems that lead to a series of adaptive changes within the myocardium collectively referred to as *LV remodelling.*

STAGES OF HEART FAILURE

Stage A: Patients at high risk for developing HF in the future but no functional or structural heart disorder;

Stage B: A structural heart disorder but no symptoms at any stage;

Stage C: Previous or current symptoms of heart failure in the context of an underlying structural heart problem, but managed with medical treatment;

Stage D: Refractory and advanced disease requiring hospital-based support, a heart transplant or palliative care.

NYHA CLASSIFICATION OF HEART FAILURE[75]

Class I (Mild)

No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).

Class II (Mild)

Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.

Class III (Moderate)

Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.

Class IV (Severe)

Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Other systems like the ESC guidelines can also be used for staging of heart failure.[55]

MECHANISMS OF HEART FAILURE

Systolic dysfunction

LV remodeling develops in response to a series of complex events that occur at the cellular and molecular levels**.** These changes include (1)

myocyte hypertrophy, (2) alterations in the contractile properties of the myocyte, (3) progressive loss of myocytes through necrosis, apoptosis, and autophagic cell death, (4) -adrenergic desensitization, (5) abnormal myocardial energetics and metabolism, and (6) reorganization of the extracellular matrix with dissolution of the organized structural collagen weave surrounding myocytes and subsequent replacement by an interstitial collagen matrix that does not provide structural support to the myocytes. The biologic stimuli for these profound changes include mechanical stretch of the myocyte, circulating neurohormones (e.g., norepinephrine, angiotensin II), inflammatory cytokines [e.g., tumor necrosis factor (TNF)], other peptides and growth factors (e.g., endothelin), and reactive oxygen species (e.g., superoxide). The sustained overexpression of these biologically active molecules is believed to contribute to the progression of HF by virtue of the deleterious effects they exert on the heart and the circulation. Indeed, this insight forms the clinical rationale for using pharmacologic agents that antagonize these systems [e.g., angiotensin-converting enzyme (ACE) inhibitors and beta blockers] for treating HF.

Diastolic dysfunction

Myocardial relaxation is an adenosine triphosphate (ATP)-dependent process that is regulated by uptake of cytoplasmic calcium into the SR by SERCA2A and extrusion of calcium by sarcolemmal pumps. Accordingly,

reductions in ATP concentration, as occurs in ischemia, may interfere with these processes and lead to slowed myocardial relaxation. Alternatively, if LV filling is delayed because LV compliance is reduced (e.g., from hypertrophy or fibrosis), LV filling pressures will similarly remain elevated at end diastole. An increase in heart rate disproportionately shortens the time for diastolic filling, which may lead to elevated LV filling pressures, particularly in noncompliant ventricles. Elevated LV end-diastolic filling pressures result in increases in pulmonary capillary pressures, which can contribute to the dyspnea experienced by patients with diastolic dysfunction. In addition to impaired myocardial relaxation, increased myocardial stiffness secondary to cardiac hypertrophy and increased myocardial collagen content may contribute to diastolic failure. Importantly, diastolic dysfunction can occur alone or in combination with systolic dysfunction in patients with HF.

DIAGNOSIS

No system of diagnostic criteria has been agreed as the gold standard for heart failure. Commonly used systems are the "Framingham criteria" (derived from the Framingham Heart Study), the "Boston criteria"[57], the "Duke criteria[58]", and (in the setting of acute myocardial infarction) the "Killip class"[59].

Framingham criteria

By the Framingham criteria, diagnosis of congestive heart failure (heart failure with impaired pumping capability) requires the simultaneous presence of at least 2 of the following major criteria or 1 major criterion in conjunction with 2 of the following minor criteria:

Major criteria[56:]

- Cardiomegaly on chest radiography
- S3 gallop (a third heart sound)
- Acute pulmonary edema
- Paroxysmal nocturnal dyspnea
- Crackles on lung auscultation
- Central venous pressure of more than 16 cm H2O at the right atrium
- Jugular vein distension
- Positive abdominojugular test
- Weight loss of more than 4.5 kg in 5 days in response to treatment (sometimes classified as a minor criteria)

Minor criteria[56]:

- Tachycardia of more than 120 beats per minute
- Nocturnal cough

- Dyspnea on ordinary exertion
- Pleural effusion
- Decrease in vital capacity by one third from maximum recorded
- Hepatomegaly
- Bilateral ankle edema

Minor criteria are acceptable only if they cannot be attributed to another medical condition such as pulmonary hypertension, chronic lung disease, cirrhosis, ascites, or the nephrotic syndrome. The Framingham Heart Study criteria are 100% sensitive and 78% specific for identifying persons with definite congestive heart failure.

Imaging

Echocardiography is commonly used to support a clinical diagnosis of heart failure. This modality uses ultrasound to determine the stroke volume (SV, the amount of blood in the heart that exits the ventricles with each beat), the end-diastolic volume (EDV, the total amount of blood at the end of diastole), and the SV in proportion to the EDV, a value known as the *ejection fraction* (EF).

In pediatrics, the shortening fraction is the preferred measure of systolic function. Normally, the EF should be between 50% and 70%; in systolic heart failure, it drops below 45%. Echocardiography can also identify valvular heart disease and assess the state of the pericardium (the connective tissue sac surrounding the heart). Echocardiography may also aid in deciding what treatments will help the patient, such as medication, insertion of an implantable cardioverter-defibrillator or cardiac resynchronization therapy.

Echocardiography can also help determine if acute myocardial ischemia is the precipitating cause, and may manifest as regional wall motion abnormalities on echo.

Chest X-rays are frequently used to aid in the diagnosis of CHF. In the compensated patient, this may show cardiomegaly (visible enlargement of the heart), quantified as the *cardiothoracic ratio* (proportion of the heart size to the chest). In left ventricular failure, there may be evidence of vascular redistribution ("upper lobe blood diversion" or "cephalization"), Kerley lines, cuffing of the areas around the bronchi, and interstitial edema.

RISK STRATIFICATION IN CHRONIC HEART FAILURE[60]

Risk stratification is prudent to determine the mortality and morbidity profile of patients with HF. It helps to identify patients who are at

low risk and therefore can be managed medically. Invasive procedures should be reserved for patients at high risk of mortality.

The following parameters are strongly associated with increased mortality in chronic heart failure and are recommended in risk stratification.

- Advanced age
- Low serum sodium
- VO_2 max (mL/kg per min <10–14)
- Low LV ejection fraction[61]
- Resuscitated sudden arrest
- NYHA functional Class III–IV
- Persistent low BP
- High serum BNP[62,71]
- Increased left ventricular volumes
- High serum creatinine
- High serum bilirubin

Studies show that low body-mass index, broad QRS[63], T-wave alternans[64], low heart rate variability, low 6 min walking ability, high left ventricular filling pressure, restrictive mitral filling pattern[65], impaired right ventricular function, high serum uric acid[66], high plasma interleukin –6[67], high

plasma oxidised LDL[68], low cardiac index, high resting heart rate and high serum norepinephrine[69] portend a bad prognosis in these patients. Recently homocysteine[70] levels are found to be associated with increased risk of heart failure. The inherent limitations associated with these factors necessitate the use of more than one factor in prognostication of chronic HF. Predictability and cost efficacy concerns have inculcated further studies in this area.

BIOMARKERS

While the diagnosis of heart failure remains based on a clinical presentation of breathlessness, fluid overload, and haemodynamic derangement, heart failure is really comprised of varied underlying pathophysiologies that carry a range of prognoses and may require a range of treatment strategies. Multi-modal imaging of the heart allows refinement of diagnosis and prognosis, yet still views cardiac failure from a macroscopic perspective. The field of 'biomarker medicine' has therefore risen in attempt to further hone our ability to classify and perhaps treat heart failure at a molecular level[72].

To date, numerous measurable serum molecules have been characterized in the context of heart failure, and these may be broadly classified as markers of inflammation, oxidative stress, extracellular

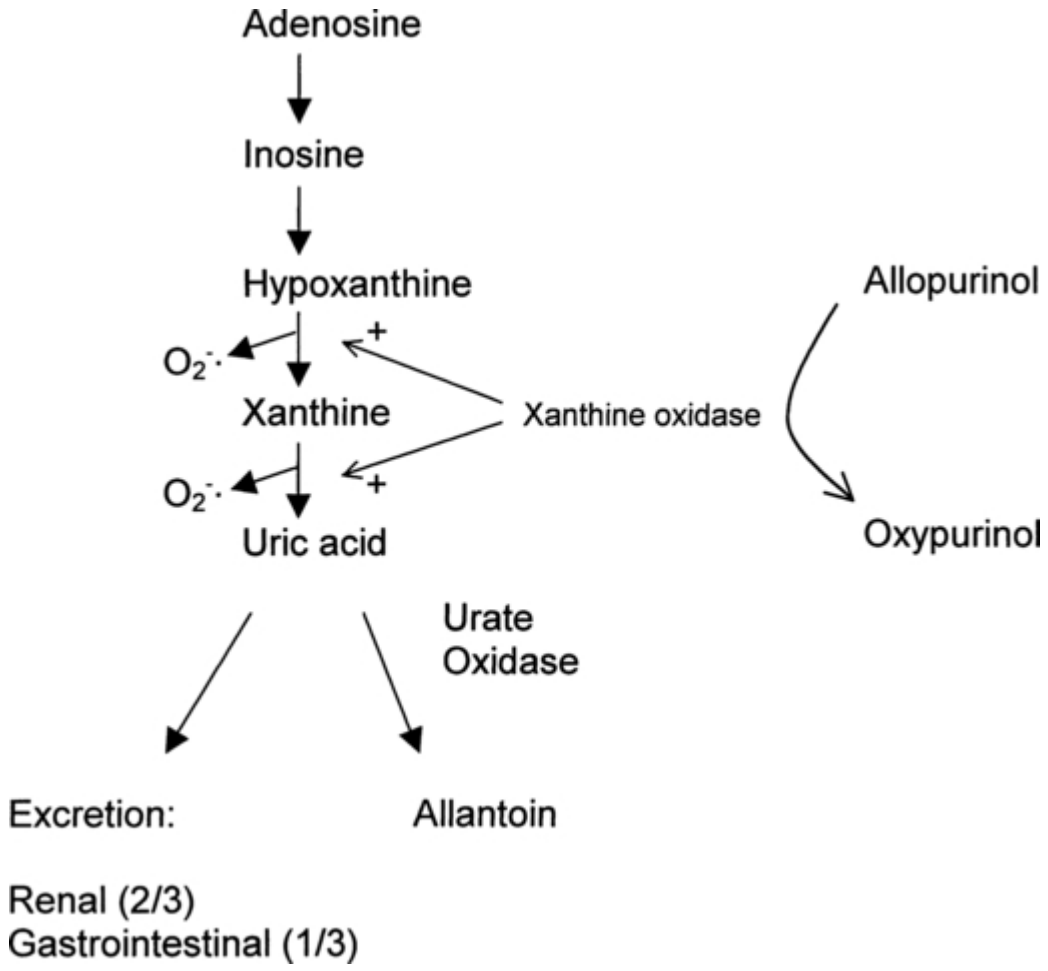
remodelling, neurohormonal activation, myocyte injury, and myocyte stress. Biomarkers should be expected to vary in relation to the underlying pathophysiology, with some being only markers of advanced heart failure, and others possibly playing a true pathophysiological role in disease progression[72].

Circulating levels of natriuretic peptides are useful adjunctive tools in the diagnosis of patients with HF. Both B-type natriuretic peptide (BNP) and N-terminal pro-BNP, which are released from the failing heart, are relatively sensitive markers for the presence of HF with depressed EF; they also are elevated in HF patients with a preserved EF, albeit to a lesser degree. However, it is important to recognize that natriuretic peptide levels increase with age and renal impairment, are more elevated in women, and can be elevated in right HF from any cause. Levels can be falsely low in obese patients and may normalize in some patients after appropriate treatment. At present, serial measurements of BNP are not recommended as a guide to HF therapy[1]. Other biomarkers, such as troponin T and I, C-reactive protein, TNF receptors, and uric acid, may be elevated in HF and provide important prognostic information[1]. Serial measurements of one or more biomarkers ultimately may help guide therapy in HF, though not currently recommended for this purpose.

URIC ACID PHYSIOLOGY AND PURINE METABOLISM IN HUMANS

Uric acid is the final breakdown product of dietary or endogenous purines and is generated by xanthine dehydrogenase (xanthine oxidase) primarily in the liver and intestine. Exogenous purines also represent an important source of uric acid, and approximately 50% of RNA purines and 25% of DNA purines are absorbed in the intestine and subsequently excreted in urine[73].

In adult humans, the uric acid pool is around 1.2g and undergoes rapid turnover, with two thirds of the uric acid pool excreted in urine. The kidneys handle urates in multiple processes, including glomerular filtration and reabsorption, secretion, and post secretory absorption in the proximal convoluted tubules[73]. The urate handling by kidneys could be affected by various factors like extra cellular volume status, urine flow rate, urine pH, urate load, and hormones[73].



In addition, several pharmacologic agents (prebenecid, salicylates, antihypertensives like angiotensin II antagonists) also influence urate excretion. Serum uric acid is also modulated by exercise, diet. However, persistent hyperuricemia typically occurs due to defective renal clearance. The limited solubility of uric acid and the absence of enzyme uricase lead to a number of clinical conditions including gout and uric acid kidney stones[73].

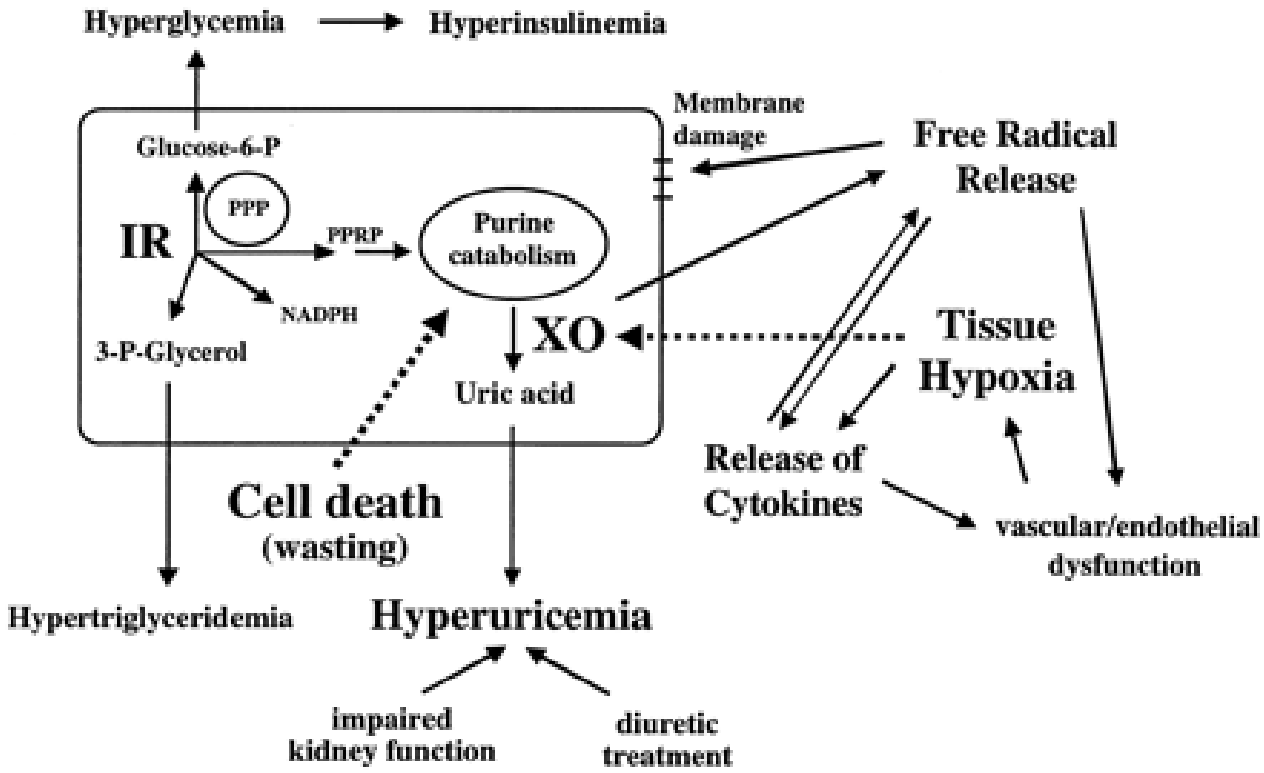
POTENTIAL MECHANISMS FOR INCREASED URIC ACID IN HEART FAILURE

UA is a metabolic byproduct of purine metabolism. Serum UA may increase in the failing circulation because of increased generation, decreased excretion, or a combination of the 2 factors. There are several possible contributors to increased UA production in HF, including increased abundance and activity of XO, increased conversion of xanthine dehydrogenase (XDH) to XO, or increased XO substrate resulting from enhanced ATP breakdown to adenosine and hypoxanthine. As UA is excreted primarily by the kidney, decreased renal perfusion could lead to increased UA levels. To the extent that HF leads to tissue ischemia (in advanced HF) and a rise in serum lactate, renal UA excretion can be further impaired as lactate competes with urate via an organic anion exchanger in the proximal tubule.

URIC ACID AND XANTHINE OXIDASE IN HEART FAILURE PATHOPHYSIOLOGY

The role of UA as an independent risk factor for the progression of HF remains unclear. To date, a clear pathophysiological link between hyperuricemia and cardiovascular complications has yet to be confirmed and UA has been related to many of the established risk factors for HF, including dyslipidemia and hypertension[48], implying that UA may instead be a marker of

increased risk. Several population studies have evaluated whether UA is an independent and causal risk factor but the evidence remains inconsistent and controversial[48].



Serum uric acid (SUA) is a byproduct of purine catabolism, the terminal steps of which are catalyzed by xanthine oxidoreductase (XOR)[74] . Serum UA may increase in the failing circulation because of increased generation, decreased excretion, or a combination of the 2 factors.

The source of uric acid in the failing heart seems supported by the fact that SUA level has been found to be elevated in the coronary sinus in HF[4] when compared with control patients.

Beyond XO activity, recent experimental studies suggest that UA itself may have a role in cardiovascular and renal pathophysiology. This might seem surprising, as UA can function as an antioxidant, both by itself and by promoting superoxide dismutase activity, [3] and might therefore be considered potentially protective. However, UA potently stimulates vascular smooth muscle cell proliferation in vitro, an effect mediated by stimulation of mitogen-activated protein kinases, cyclooxygenase-2, and platelet-derived growth factor. Furthermore, rats with mild experimentally induced hyperuricemia develop intrarenal vascular disease with increased renin expression, systemic and glomerular hypertension, and renal injury in the absence of intrarenal crystal deposition[16,15].

Data from several experimental animal studies indicate that hyperuricemia is associated with the down-regulation of nitric oxide (NO) in endothelial smooth muscle through an increase in reactive oxygen species (ROS)[6]. ROS reduces the bioavailability of endothelial NO and leads to endothelial dysfunction through a loss in NO-dependent vasodilation.[6] Meanwhile, UA is a potent antioxidant that might counteract the effect of ROS,

but there is evidence that hyperuricemia by itself reduces the abundance of NO-synthase and impairs NO-mediated vasodilation.[24]

Accumulating data also suggest that UA, aside from being a potentially valuable prognostic marker, possesses certain toxic or other effects that may contribute to HF pathophysiology beyond a reflection of increased XO activity. Experimental studies in animals have reported that UA is a potent stimulator of intrarenal vascular smooth muscle cell proliferation,[26] an effect that may lead to significant hemodynamic changes in the failing circulation.

Human atherosclerotic plaque has been shown to contain a considerable amount of uric acid, and hyperuricemia may promote thrombus formation via purine metabolism[20]. In addition, increased uric acid concentrations are associated with the increased production of oxygen free radicals, promote oxygenation of LDL cholesterol, and facilitate lipid peroxidation [20]. Each of these factors is known to play a crucial role in the progression of atherosclerosis.

FACTORS THAT AFFECT URATE LEVEL

Dietary Habits

An increase in serum urate level may occur in purine rich diet such as Non-vegetarian diets – liver, anchovies, kidneys, sardines and sweet breads and yeasts.

Exercise

Exercise acutely increases serum urate levels by excessive degradation of skeletal ATP.

Alcohol

Alcohol increases serum urate level by accumulation of organic acids (beta hydroxyl butyrate, aceto-acetate, lactate) that compete with the urate for tubular secretion and accelerated breakdown of ATP by liver is increased. (Beer contains high uric acid)

Obesity

Various mechanisms play role in increase of serum urate by obesity, like anabolic effects of tissues because of insulin resistance, increase in de novo biosynthesis of purines, decreased excretion and increased breakdown.

Dehydration

Dehydration can impair uric acid excretion by decreased filtration and secretion and sometimes with the acidosis by competition of H+ ions for excretion. Starvation again causes accumulation of organic acids that compete for the excretion of urate for tubular secretion.

Systemic Hypertension

There are various studies regarding association of systemic hypertension with the elevated uric acid levels. Probable mechanism suggested is impaired excretion of urate because of intrinsic renal defect in HT.

Hyperglycemia

Both uric acid and glucose levels are positively related to body mass index. The association of uric acid in relation to glucose reflects the biochemical interaction between serum glucose and purine metabolism. (Deranged carbohydrate metabolism)

Renal Insufficiency

Decreased urate filtration contributes to the hyperuricemia of renal insufficiency. But the correlation between BUN, serum creatinine and serum uric acid concentration is poor because although uric acid excretion per unit of

GFR increases progressively with renal insufficiency, the tubular secretory capacity tends to be preserved, the tubular reabsorptive capacity is decreased and extrarenal clearance of uric acid increases as the renal damage becomes more severe.

Drugs

They mainly act by decreasing the uric acid excretion by competitive inhibition of uric acid excretion. Salicylates and nicotinic acid directly compete with the urate for tubular secretion. Diuretics decrease the secretory capacity and increase reabsorption. L-Dopa, pyrazinamide, ethambutol, cyclosporine also decrease the secretion of urate by the tubules.

URIC ACID IN CARDIOVASCULAR DISEASE

Uric acid has often been considered a part of the dysmetabolic syndrome or simply a marker of other coronary disease risk factors such as hypertension, dyslipidemia, glucose intolerance and renal diseases.

However, most epidemiological studies have demonstrated a significant association between serum uric acid and CV morbidity and mortality. Serum levels are associated with the occurrence of stroke and MI (myocardial infarction) as well as all CV-related events. The link has been

studied in the general population as well as in persons with diabetes mellitus, congestive heart diseases, angiographically confirmed coronary artery diseases (CAD) and hypertension[50]. Hyperuricemia is frequently encountered in hypertensive patients and may occur due to a defect in renal urate clearance. Patients with hypertension and hyperuricemia have a 3 to 5 fold increased risk of experiencing coronary artery disease or cerebrovascular disease compared with patients having normal uric acid levels[51].

URIC ACID AS A PROGNOSTIC MARKER IN HEART FAILURE

Numerous parameters are capable of predicting prognosis in patients with chronic heart failure (CHF). Many of the modern parameters are only assessed by using research tests that are not widely available. There is a need for simple parameters that can be measured anywhere at low cost. Very few attempts have been made to develop scoring systems to predict prognosis in patients with CHF[50,51], but these are not simple enough for general application. For prognostication in CHF, the following 3 main areas of relatively independent importance emerge: (1) a hemodynamic factor (for example, left ventricular ejection fraction [LVEF]); (2) the patient's functional status (eg, peak oxygen consumption [$\dot{V}O_2$]); and (3) a metabolic factor, including the neuroendocrine and immunologic processes.[52]

In patients with heart failure, high levels of serum uric acid are highly predictive of mortality and are useful in identifying the need for aggressive intervention. A graded relationship has been observed between serum uric acid and mortality in heart failure patients. These highlight the prognostic importance of serum uric acid along with other clinically established parameters.

Patients with angiographically confirmed CAD with serum uric acid levels in the upper quartile were found to be five times more prone to mortality[52]. A 1-mg/dL increase in serum uric acid levels was associated with 26% increase in mortality[4]. A study of Type II Diabetes mellitus showed that stroke incidence significantly increased by quartiles of serum uric acid levels and that high serum uric acid levels were significantly associated with risk of both fatal and nonfatal strokes. The increased risk was apparent even when other risk factors were taken into account.

UA has also been identified as an effective predictor in several multiparametric HF models, such as the Seattle Heart Failure Model[19] and, also, the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure (SENIORS) model. In both of these models, the predictive value of UA was independent of renal function, which was excluded from the Seattle Heart Failure model altogether. This

raises the important question of whether UA is a more useful prognostic factor than renal function and whether it should be included in conventional prognostic assessments of HF patients.

SUA is a routinely measured variable in clinical laboratories, with repeatable results and nonsignificant short-term individual fluctuations without any age-specific or diurnal patterns[20.] Given these characteristics, SUA could feasibly be used as a helpful prognostic indicator in clinical practice.

XANTHINE OXIDASE INHIBITION AND HEART FAILURE OUTCOMES

Recent clinical trials have suggested that XO inhibition may lead to improved mechanics and better clinical outcomes in patients with congestive HF (CHF). Numerous studies have reported that lowering UA levels improves endothelial reactivity[49], myocardial function[5], and ejection fraction[47] in patients with CHF and may lead to better clinical outcomes in a subgroup of HF patients with high SUA levels[22].

Early clinical trials supported a role for UA in the loss of endothelium-dependent vasodilation in patients with CHF. After an initial study in 19 men with CHF, which reported that infusion of allopurinol improved endothelium-dependent vasodilation in hyperuricemic patients, a double-blind cross-study was performed in 14 men by *Doehner, Anker* et al

with hyperuricemia and CHF.[42] When compared with placebo, treatment with allopurinol improved peak blood flow in the arms and legs while reducing levels of both UA and allantoin, a marker of oxygen-free radical generation. These findings were replicated in a second randomized, placebo-controlled, double-blind cross study in 11 patients with New York Heart Association (NYHA) class II or II CHF[43] by *Reyes* et al. In this trial, daily treatment with allopurinol also led to improved endothelial-dependent vasodilation while reducing levels of plasma maldondialdehyde, another maker of oxidative stress.

In both studies, the proposed mechanism was through an increase in the bioavailability of endothelium-derived NO, presumably by blocking the production of ROS produced by XO activity, as evidenced by the significant reduction in plasma biomarkers for oxidative stress. This hypothesis has been supported by several recent studies.

A recent preliminary, double-blind, placebo-controlled crossover study by *Ogino* and associates,[48] UA lowering with the uricosuric agent benzbromarone in 14 patients with CHF and hyperuricemia did not improve hemodynamic impairment although SUA levels decreased significantly. These findings suggest that up-regulated XO activity rather than UA itself is involved in CHF pathophysiology and that the mechanism of

improvement with allopurinol may lie in its ability to reduce oxidative stress and not SUA levels.

From a functional standpoint also, XO inhibition may lead to improvements in cardiac performance. An early study by *Cappola* and coworkers[5] in patients with dilated cardiomyopathy, treatment with intracoronary allopurinol led to a significant decrease in myocardial oxygen consumption with no parallel decrease in stroke work, yielding a substantial improvement in myocardial efficiency. More recently, the *La Plata Study*[47], a randomized, placebo-controlled, double-blind study in 60 patients with NYHA II or III CHF, demonstrated the ability of oxypurinol to improve left ventricular ejection fraction (LVEF) in patients with a baseline LVEF <40%. By potentially reversing the energetic inefficiency and improving the cardiac output of the failing circulation, pharmacologic XO inhibition may represent a novel therapeutic option for the treatment of HF.

To the extent that XO inhibition may lead to improvement in clinical outcomes, the Efficacy and Safety Study of Oxypurinol Added to Standard Therapy in Patients With New York Heart Association Class III-IV Congestive Heart Failure *(OPT-CHF)* study randomized 405 patients with moderate to severe CHF due to systolic dysfunction to either oxypurinol or placebo.[22] Using a composite end point of HF morbidity, mortality, and quality of life, oxypurinol

did not produce clinical improvements in unselected patients at 24 weeks. However, post hoc analysis suggested that patients with elevated levels of SUA (>9.5 mg/dL) might represent a responsive group, as there was a trend towards benefit in patients who received oxypurinol in this subgroup. Interestingly, the response to oxypurinol, as indicated by SUA reduction, correlated with the degree of clinical outcome in the high SUA group. Together, these findings suggest that SUA can serve as a valuable biomarker to target XO inhibition for select patients with HF, and does so in a manner that correlates with the degree of SUA reduction.

MATERIALS AND METHODS

Study design

Case control study

Setting

All patients were prospectively enrolled from the Cardiology and Internal medicine department of Government General Hospital, Chennai 3.

Sample

100 patients with clinical evidence of heart failure were enrolled in this study. All patients had documented evidence of heart failure and were on heart failure treatment for at least one month. Informed consent was obtained from all patients. 40 age and sex matched controls were selected.

Inclusion criteria

Patients of both sex aged between 20 to 80 years

Patients with Heart failure both with preserved and decreased EF.

Patients with Heart failure of atleast 1 month duration

Exclusion criteria

Patients with pre existing gout and heart failure

Patients on long standing diuretics and heart failure

Chronic kidney disease

Haematological malignancy

ATT –Pyrazinamide

Procedure

A questionnaire prepared noted the duration, symptoms and treatment of heart failure. Questions were asked in relation to chest pain, dyspnoea, syncope, cough, smoking and medications. All previous clinical records of the patients were analyzed in detail. Based on the degree of effort needed to elicit symptoms, patients were assigned to NYHA class I to IV of heart failure. A detailed physical examination was conducted to assess patients' volume status (rales, edema, jugular venous distension), weight, height, body mass index and orthostatic blood pressure changes. Complete blood count, blood glucose (fasting and 2 hour post prandial), fasting serum lipid profile, blood urea, serum creatinine and serum electrolytes were measured in all patients. Two-dimensional echocardiography was done in the cardiology department of Government General Hospital for all patients. Serum uric acid levels were measured on admission for all the 100 patients who met the inclusion criteria and compared with 40 age and sex matched controls.

Statistical significance was made out using the t test. Patients were followed up for a period of 30 days and prognosis was assessed by noting down symptomatic improvement or mortality.

Instruments

1. Electrocardiogram:

All patients had 12 lead ECG, which was reviewed for evidence of atrial enlargement, ventricular hypertrophy, evidence of antecedent myocardial infarction and conduction blocks.

2. Chest x ray:

Chest x ray posteroanterior view was done in all patients to note pulmonary congestion, pleural effusion and to estimate cardio thoracic ratio.

3. Echocardiography:

M-mode echocardiography was used to assess left ventricle dimensions. Left ventricle internal dimension in end systole (LVESD) and end diastole (LVEDD) were measured at the level of mitral valve leaflet tips in parasternal long axis view. Measurements were taken from the endocardium of the left surface of the interventricular septum to the endocardium of the left ventricle posterior wall. In adults the normal range of LVEDD is 3.5 to 5.6 centimeter. The normal

range of LVESD is 2 to 4 centimeter[59.] 2-D echo imaging in apical 4 chamber, parasternal long axis and parasternal short axis views were used to assess ventricular and valvular movement. Ejection fraction was estimated using Simpson's method[60]. In this method multiple short axis views are taken along the LV long axis. Endocardial border is traced accurately and left ventricle cavity is divided into 20 slices of known thickness and diameter (D). Left ventricle end diastole and Left ventricle end systole volumes are estimated.

Area of each slice=22/7 (D/2)2

Volume of each slice = area X thickness.

LV volume= volume of each slice X number of slices (20)

$$EF = \frac{\text{(Left ventricle end diastole volume - Left ventricle end systole volume)} \times 100}{\text{Left ventricle end diastole volume}}$$

Laboratory methods

Fasting plasma glucose was measured using glucose oxidase and pyruvate oxidase methods from overnight fasting sample and results were

read by autoanalyser.2 hr postprandial glucose was measured 2 hrs after routine morning breakfast.

From patients height and weight, body mass index (BMI) was calculated using the formula weight in kilograms divided by square of height in meters.

Serum cholesterol (enzymatic oxidase-peroxidase method), Serum HDL (polyethylene glycol-CHOD-PAP method) Triglycerides (enzymatic calorimetric method) were measured using Erba XL 300 autoanalyser. Serum LDL was calculated using Friedewald's formula[61].

1. Estimation of uric acid

It is the most oxidised member of the purine class of compounds. Further oxidation of uric acid in alkaline solution results in disruption of purine ring with removal of carbon 6 as carbon dioxide and formation of allantoin and other degradation compounds. Alloxan is the product of uric acid oxidation in acid solution. With addition of ammonia it forms ammonium purpurate, purplish red substance responsible for the well known murexide test for uric acid, produced by heating uric acid and adding a few drops of ammonium hydroxide. Other Calorimetric methods for uric acid estimation are based on reducing properties of uric acid.

Method: Uricase method

Principle:

Uricase converts uric acid to allantoin and hydrogen peroxide. The hydrogen peroxide formed further reacts with phenolic compound and 4-Amino antipyrine by the catalytic action of peroxidase to form a red coloured quinoneimine dye complex. Intensity of the colour formed is directly proportional to the amount of uric acid present in the sample.

Uric acid + H_2O → Allantoin + H_2O_2

H_2O_2 + 4- Amino antipyrine + Phenolic compound → Red quinoneimine dye + H_2O

Normal values:

Serum Uric Acid (males) = 3.0 to 7.0 mg/dl

Serum Uric Acid (females) = 2.5 to 6.0 mg/dl

2. Dyslipidemia[76]

Any one of

Serum total cholesterol >/= 200 mg/dl (Borderline High)

Serum HDL </= 40 mg/dl(low)

Serum triglycerides >/= 200 mg/dl (High)

Serum LDL >/= 160 mg/dl(High) (ATP III guidelines)

3. Diabetes mellitus[77]

1. Plasma glucose of 126mg/dl or greater after overnight fasting

2. Post prandial Plasma glucose of 200 mg/dl or greater

3. Symptoms of DM with random glucose 200 mg/dl or greater

4. HbA1C > 6.5%

4. Systemic hypertension

Based on JNC 8 classification systolic BP of 140 mm Hg and above and diastolic BP of 90 mm Hg and above was defined as systemic hypertension.

5. Obesity

Obesity is defined as body mass index more than 30 kg/m^2.

Statistical analysis:

Following statistical methods have been employed in the present study.

- Independent samples ‘t’ test-Unpaired.
- Independent samples ‘t’ test-Paired.
- One-way Analysis of Variance (ANOVA).
- Pearson correlation coefficient.
- Relative risk.

The study was approved by the ethics committee of the hospital

RESULTS

Table 1: Age incidence

AGE	NO.OF PATIENTS	%
20 to 30	4	4
30 to 40	15	15
40 to 50	34	34
50 to 60	27	27
60 to 70	20	20

In the study group of 100 patients with heart failure, 34% were in the age group of 40-50, 27% in the age group of 50-60, 20% in the age group of 60-70, 4% in the age group of 20-30 years.

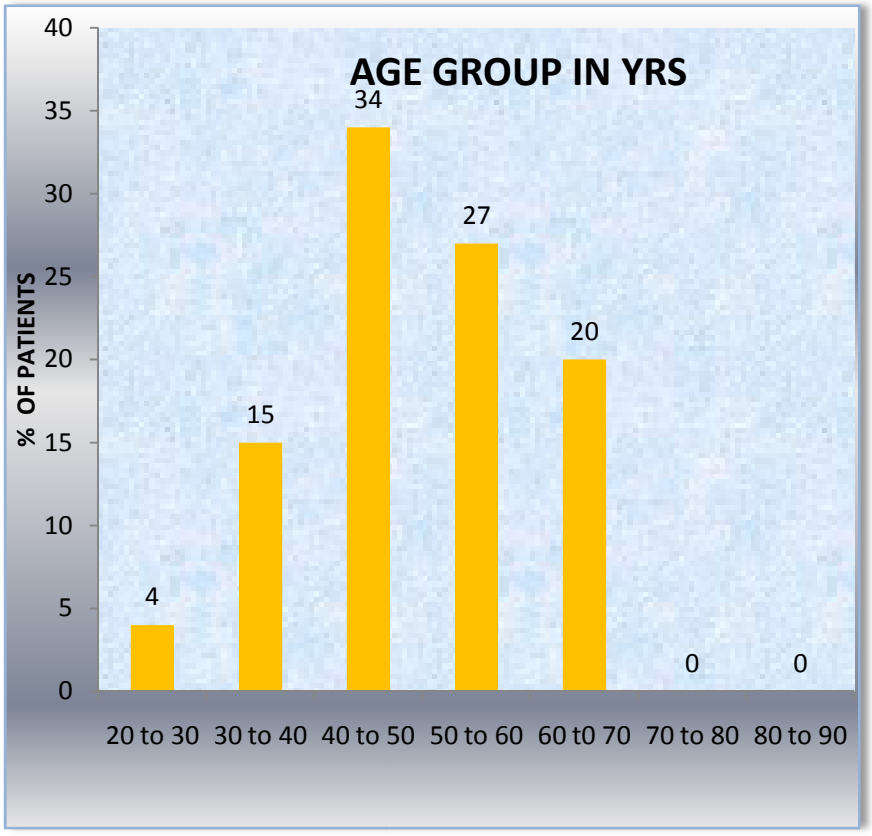


Table 2 : Age and sex incidence

AGE GROUP (Yrs)	NO. OF PATIENTS				TOTAL	
	MALE		FEMALE			
	No.	%	No.	%	No.	%
20 to 30	0	0	4	9	4	4
30 to 40	9	15	6	14	15	15
40 to 50	24	40	10	24	34	34
50 to 60	13	20	14	34	27	27
60 to 70	13	22	7	17	20	20
70 to 80	0	0	0	0	0	0
80 to 90	0	0	0	0	0	0
Total	59	100	41	100	100	100

In the study group of 100 patients with heart failure, 59% were males and 41% were females. Male:Female ratio was 1.43:1. In both males and females maximum incidence was seen in the age group of 40-50 years.

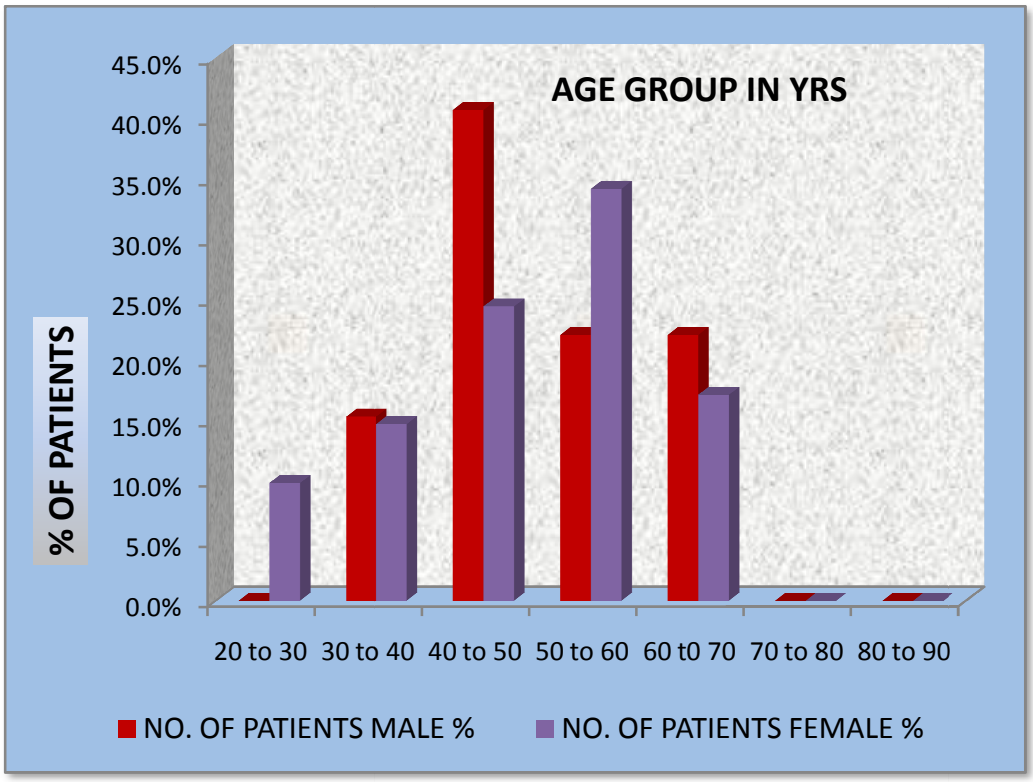


Table 3 :Type of heart failure and no. of patients

CAUSE OF HEART FAILURE	NO. OF PATIENTS				TOTAL	
	MALE		FEMALE			
	NO	%	NO	%	NO	%
CAD	28	47	20	49	48	48
RHD	6	10	8	20	14	14
COPD/COR PULMONALE	11	19	1	2	12	12
CALCIFIC AS/AR	2	3	2	5	4	4
EISENMENGER SYN.	1	2	2	5	3	3
DCM-CAUSE UNKNOWN	4	7	4	10	8	8
ALCOHOLIC C.MYOPATHY	2	3	0	0	2	2
RVD	5	8	0	0	5	5
PERIPARTUM C.MYOPATHY	0	0	4	10	4	4
TOTAL	59	100	41	100	100	100

100 patients of heart failure were studied, among them, 59% were males and 41% were females. Of the males 47% had CAD, 19% had COPD/cor pulmonale, 10% had RHD, 7% had DCM-unknown cause. Among the females 49% of CAD, 20% had RHD, 10% had DCM unknown cause and 10% had peripartum cardiomyopathy.

Chart showing the distribution of various causes for heart failure:

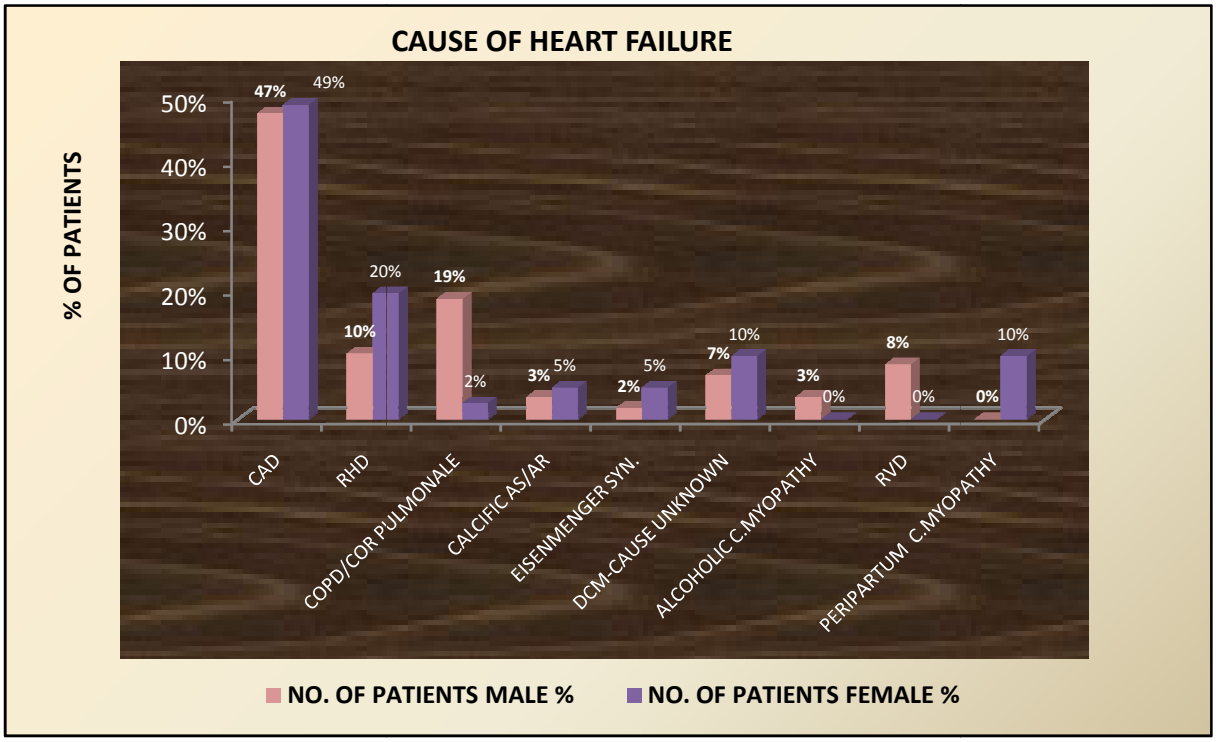


Chart showing the various causes of heart failure in both men and women:

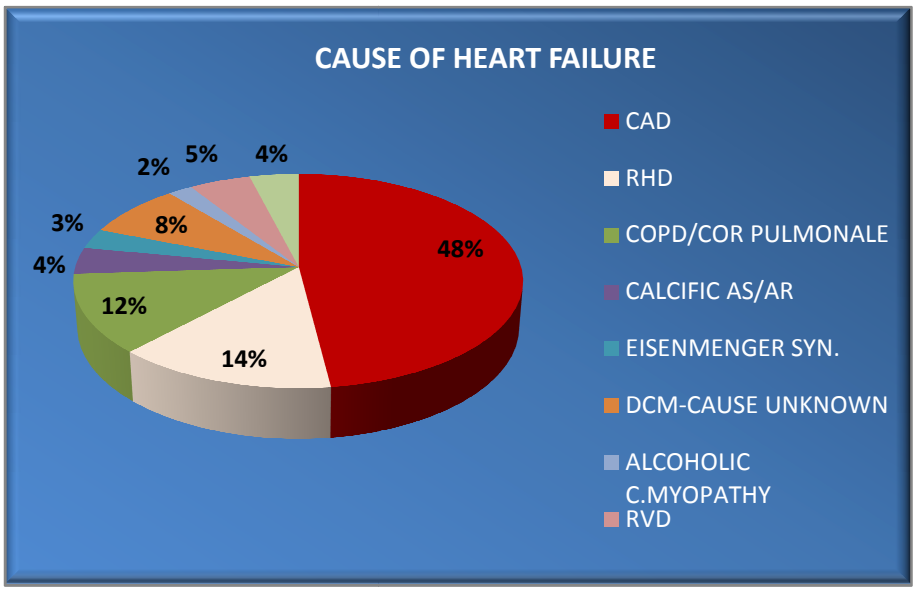


Chart showing the various causes of heart failure in men:

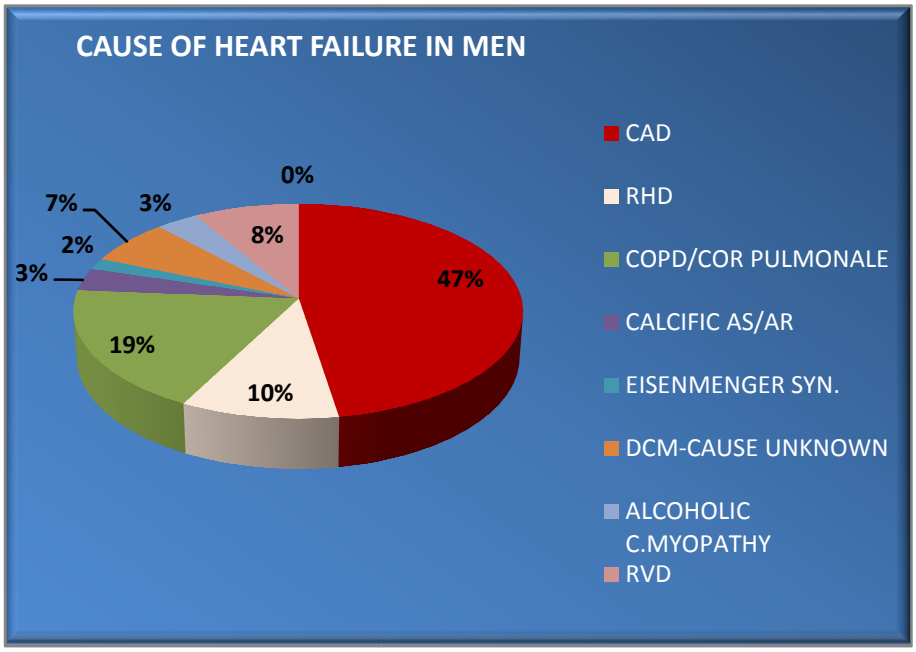


Chart showing the various causes of heart failure in women:

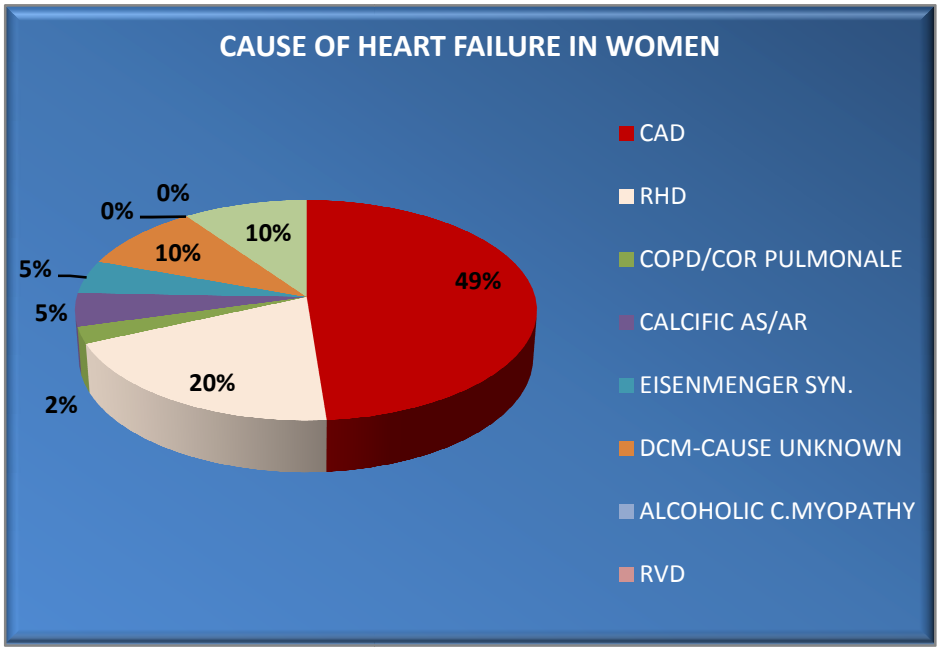


Table 4: Major risk factors

MAJOR RISK FACTORS IN PATIENTS WITH HEART FAILURE						
	NO. OF PATIENTS					
	MALE No.=59		FEMALE No. = 41		TOTAL	
RISK FACTORS	NO	%	NO	%	NO	%
SMOKING	41	69%	0	0%	41	41%
ALCOHOLISM	32	54%	0	0%	32	32%
HYPERTENSION	25	42%	13	32%	38	38%
DIABETES	21	36%	14	34%	35	35%
DYSLIPIDEMIA	18	31%	11	27%	29	29%

Out of the 100 patients studied, smoking was present in 41% of patients, hypertension in 38% of patients, diabetes mellitus in 35% of patients.

Chart showing the various risk factors for development of heart failure:

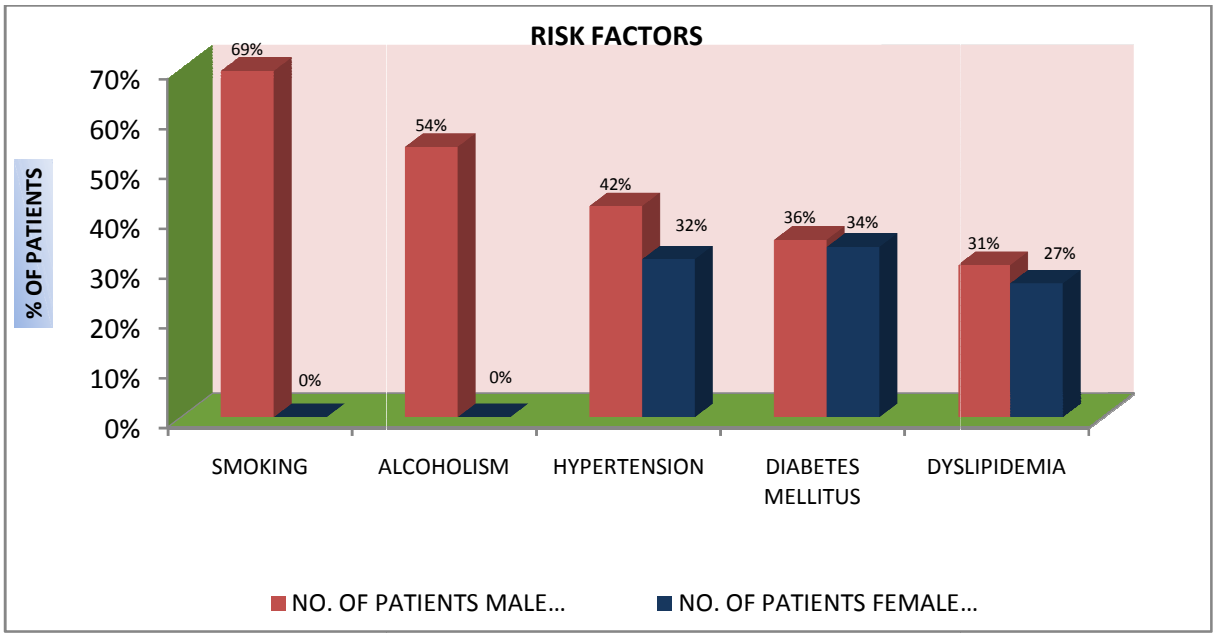
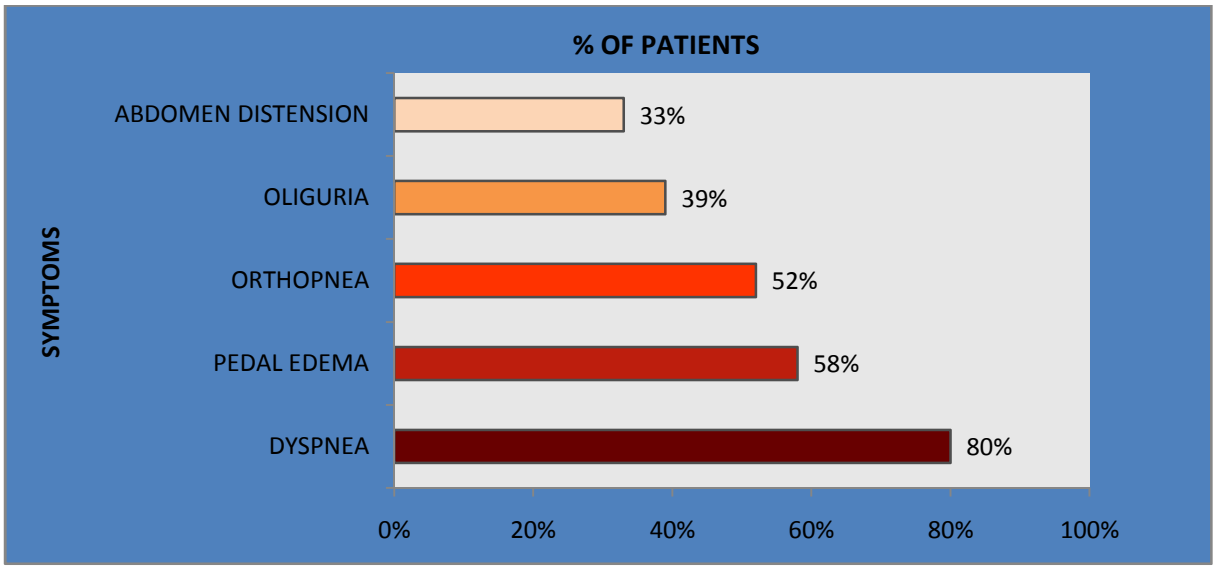


Table 5:Major symptoms

SYMPTOMS	NUMBER OF PATIENTS	%
DYSPNEA	80	80%
PEDAL EDEMA	58	58%
ORTHOPNEA	52	52%
OLIGURIA	39	39%
ABDOMEN DISTENSION	33	33%
TOTAL	100	100 %

Among 100 patients 80% had dyspnea, 58% had pedal edema, 52% had orthopnea, 39% had oliguria and 33% had abdominal distension

Chart showing the various symptomatology:



We have studied 100 patients with heart failure and 40 age and sex matched controls. Their comparative uric acid levels are given in the table below:

Table 6: Uric acid levels in patients and controls

PARAMETER	PATIENTS No.= 100	CONTROLS No. = 40	P VALUE
AGE	50 ± 19	47 ± 24	0.179 (NS)
SR URIC ACID	6.35 ± 5	3.6 ± 1	0.0001 (S)

There was a statistically significant higher level of uric acid concentration in patients of heart failure as compared to controls (P<0.05).

Chart showing mean serum uric acid levels in patients and controls:

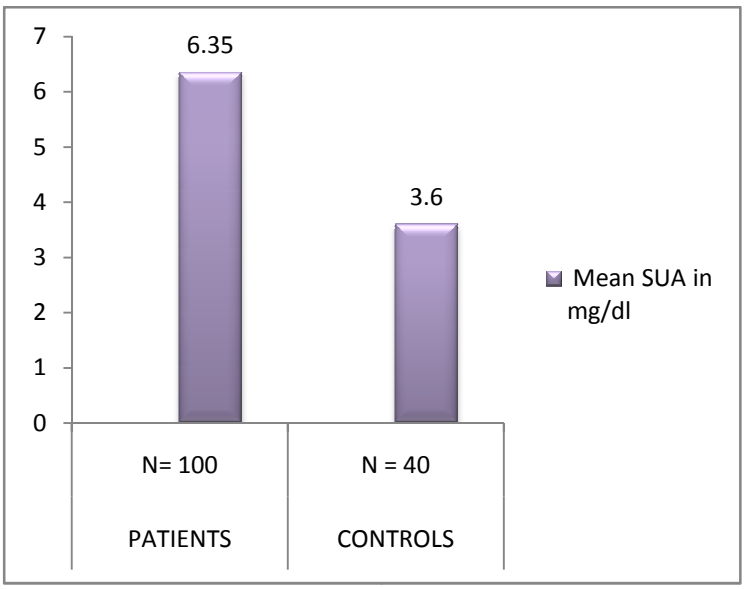


Table 7: Patient profile and serum uric acid levels

PARAMETER	GROUP I	GROUP II	P VALUE
SEX	MALE NO.=59	FEMALE N0. = 41	
SR URIC ACID ON ADMISSION	7.4 ± 4	4.8 ± 3	0.0001 (S)
HYPERTENSION	YES : 38	NO : 62	
SR URIC ACID	6.2 ± 4	6.4 ± 5	0.7483 (NS)
DIABETES MELLITUS	YES : 35	NO : 65	
SR URIC ACID	6.2 ± 3.8	6.4 ± 4.8	0.9255 (NS)

There was no significant difference in serum uric acid levels as regards hypertension and diabetes mellitus in patients with heart failure, but there was a statistically significant difference in serum uric acid levels (p=0.0001) in male patients when compared to females.

Chart showing the mean serum uric acid levels in males and females:

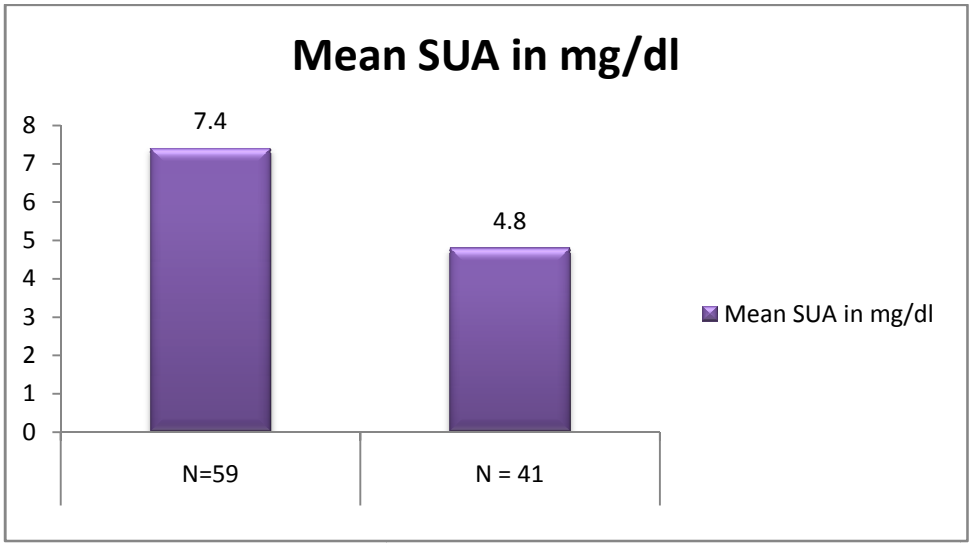


Table 8:Dyslipidemia and uric acid levels

Dyslipidemia	Present(No.=29)	Absent(No.=71)
Mean SUA	7.16	6.01

Dyslipidemia was present in 71 % of the individuals and it was absent in 29% of the individuals. The mean serum uric acid was 7.16 mg/dl in those with dyslipidemia and 6.01 mg/dl in those without dyslipidemia. The mean serum uric acid between the two groups was compared by the unpaired t test and it was found that the p value was > 0.9999 and it was not significant.

Chart showing the mean serum uric acid level in patients with dyslipidemia:

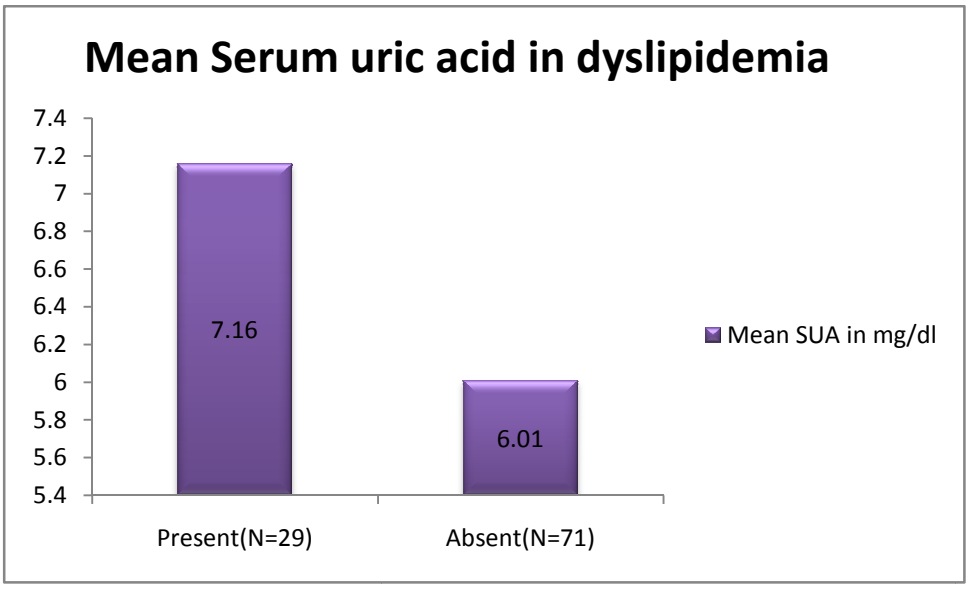
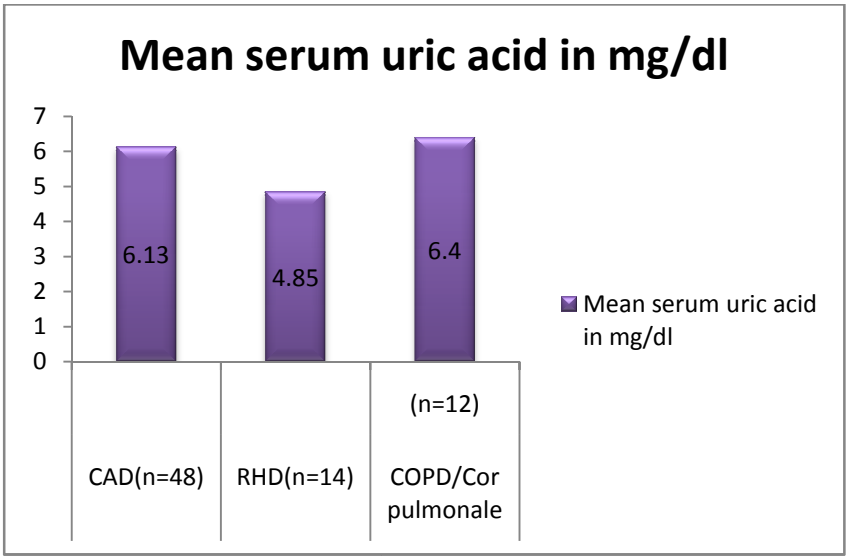


Table 9.Comparison of uric acid levels with causes of heart failure

CAUSE OF HEART FAILURE	CAD(n=48)	RHD(n=14)	COPD/Corpulmonale (n=12)
Mean serum uric acid in mg/dl	6.13	4.85	6.4

The mean serum uric acid levels were compared among the three common causes of heart failure encountered in the study. It was found that the p value was 0.05 and it was not that significant using the ANOVA test.

Chart showing the mean serum uric acid levels in various causes of heart failure:



To find out correlation between duration of heart failure and serum uric acid Pearson's coefficient was used and the results were as follows:

Correlation coefficient (r) = -0.05287

95% confidence interval: -0.2468 to 0.1451

Coefficient of determination (r squared) = 0.002795

The two-tailed P value was 0.6014, considered not significant.

Hence it was inferred that there was no correlation between duration of heart failure and levels of serum uric acid.

Table 10: Uric acid in correlation with NYHA Class of heart failure

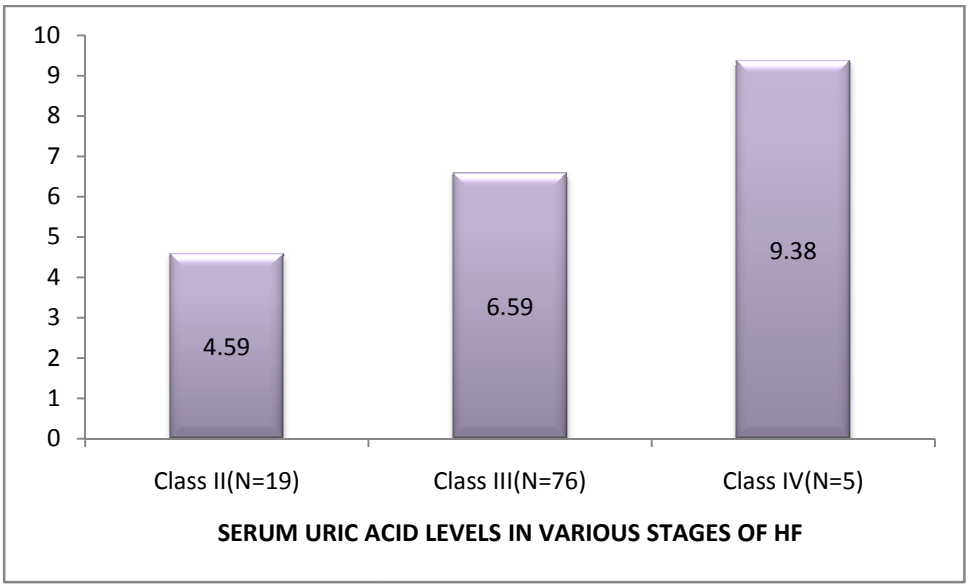
NYHA Class of heart failure	Class II(N=19)	Class III(N=76)	Class IV(N=5)
Mean Uric acid	4.59	6.59	9.38
Standarddeviation	1.8914	1.832	1.892

Comparison	Mean difference	q	P value
Class II vs Class III	-2.010	4.486	P<0.01
Class II vs Class IV	-4.800	7.232	P<0.001
Class III vs Class IV	-2.790	4.124	P<0.05

According to the Tukey-Kramer Multiple Comparisons Test if the value of q is greater than 3.455 then the P value is less than 0.05.

Among the 100 patients 19 were in class II HF, 76 patients were in class III HF and 5 were in class IV HF. The serum uric acid among the three groups was compared using the ANOVA test and was found to be statistically significant. The P value was < 0.0001, considered extremely significant. Variation among column means was significantly greater than expected by chance. Patients in class IV HF had higher uric acid levels than those on class III and class II HF.

Chart showing the serum Uric acid levels in correlation with NYHA Class of heart failure:



To find out correlation between Ejection fraction and serum uric acid Pearson's coefficient was used and the results were as follows:

Correlation coefficient (r) = -0.1739

95% confidence interval: -0.3581 to 0.02341

Coefficient of determination (r squared) = 0.03023

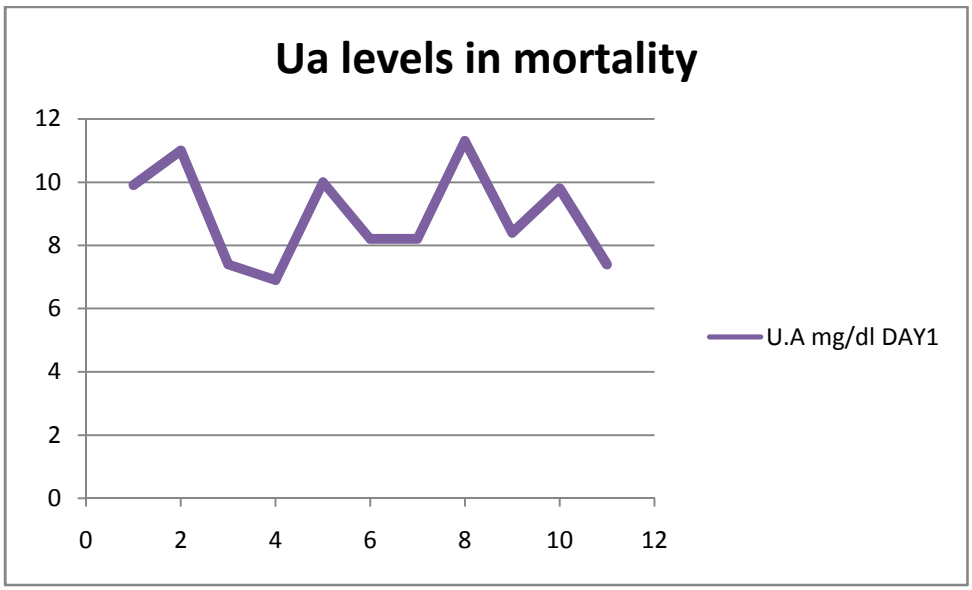
The two-tailed P value was 0.0836, considered not quite significant. Hence it was inferred that there was no correlation between Ejection fraction and serum uric acid.

Table 11.Uric acid levels before and after treatment of HF

PARAMETER	UA BEFORE TREATMENT No.= 100	UA AFTER TREATMENT No. = 100	P VALUE
MEAN SR URIC ACID	6.35	6.04	0.1756(NS)

The mean serum uric acid levels of the patients were compared before and after treatment of HF and it was found that p >0.05, not significant.

Out of the 100 patients, 20 patients were lost follow up and in the remaining 80 patients 13 Patients expired.0ut of the 13 patients 11 had higher uric acid levels. 5 of them were in class IV heart failure and 6 were in stage III heart failure with mean uric acid level of 8.9 mg/dl. This graph below depicts the uric acid levels in those who expired.

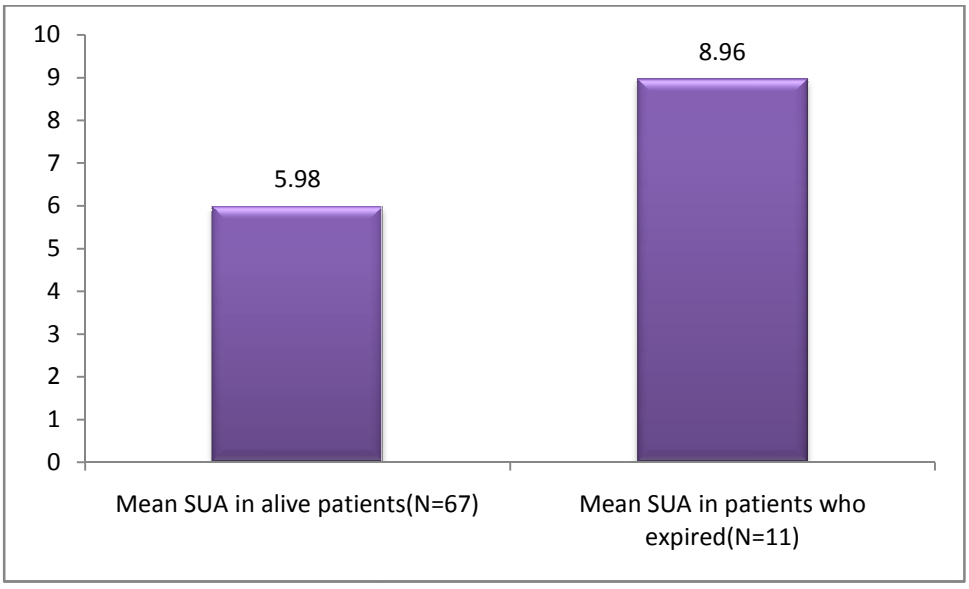


It was found that mean uric acid level was 8.9 mg/dl in those who expired.

Table 12.Serum uric acid level in patients in comparison with mortality and survival

Mean SUA in alive patients(N=67)	Mean SUA in patients who expired(N=11)	
5.98	8.96	P value <0.001(s)

Serum uric acid level in patients in comparison with mortality and survival :



The mean serum uric acid level between those patients who are alive were compared with those who expired and it was found significant with p value <0.05.

DISCUSSION

Elevated SUA levels have been associated with an increased risk for cardiovascular disease.[29] Serum uric acid level is an index of oxidative stress in the human body[30]. Serum uric acid is known to contribute to endothelial dysfunction by impairing nitric oxide production.[31] Serum uric acid has also been shown to be inversely correlated with the measures of functional capacity and maximal oxygen intake. Among patients with chronic heart failure, serum uric acid concentrations are associated with greater activity of superoxide dismutase and endothelium-dependent vasodilatation.[32]

Another potential pathophysiological link between hyperuricemia and heart failure might be through inflammation. Asymptomatic hyperuricemia is a proinflammatory state associated with higher levels of serum markers of inflammation, such as C-reactive protein, interleukin-6, and neutrophil count.[31,33,34] Among patients with heart failure, hyperuricemia is associated with higher levels of markers of endothelial activation, such as the soluble intercellular adhesion molecule-1, and inflammatory markers such as interleukin-6, tumor necrosis factor-α, and its receptors. Similar observations have been made in some population-based studies[35] and hospital-based studies. The risk of heart failure was proportionate to the degree of elevation

of serum uric acid among patients with gout.[36] Locally, even when there is no active arthritis, the synovial fluid of patients with gout shows low-grade inflammatory activity.[37]

Increased levels of serum uric acid among normal individuals predict hypertension,[27,38] renal dysfunction,[25] and coronary artery disease[22] and portend reduced life expectancy.[39] Lowering of serum uric acid with allopurinol can reduce blood pressure among hypertensives.[40,41] This raises the possibility of the hyperuricemia-heart failure link being mediated by hypertension, a hypothesis that cannot be directly tested in observational studies. Nevertheless, some studies have shown that hyperuricemia is an independent risk factor for heart failure among those who already have hypertension.

We have studied 100 patients with heart failure and 40 age and sex matched controls. These patients were admitted to our hospital during June to November 2011. Their comparative uric acid levels are given in the table above.

The mean age group of patients with heart failure found in our study was 50 years with the minimum age of 27 years and the maximum age of 69 years. Out of the 100 patients of heart failure 59% were males and 41% were females. The mean age in men was found to be 50 years and in women was found to be 49.41 years.

40 controls were selected from patients admitted for other causes like fever and from healthy volunteers. Controls did not have any co-morbid illness. The mean age among controls was 47 years. To find out if the controls' age differed from that of the patients the unpaired t test was used and it was found that the P value was 0.1714 considered not significant. The male:female ratio among controls and patients were similar the results being 1.5:1 and 1.45:1 respectively. In both males and females maximum incidence was seen in the age group of 40-50 years

The mean serum uric acid found in our study was 6.35 mg/dl as compared to the control value of 3.61 mg/dl. The mean uric acid in men was 7.4 mg/dl and in women it was 4.83 mg/dl. There was no correlation between age and serum uric acid made in our study.

Of the males 47% had CAD, 19% had COPD/ cor pulmonale, 10% had RHD, 7% had DCM-unknown cause. Among the females 49% of CAD, 20% had RHD, 10% had DCM unknown cause and 10% had peripartum cardiomyopathy. The most common cause for HF was found to be CAD in our study. Our study did not find any correlation between EF and serum uric acid levels and also between duration of heart failure and uric acid levels.

Among 100 patients 80% had dyspnea, 58% had pedal edema, 52% had orthopnea, 39% had oliguria and 33% had abdominal distension. So according to our study dyspnea was the most common symptom which necessitated hospitalisation.

There was no significant difference in serum uric acid levels as regards hypertension and diabetes mellitus in patients with heart failure, but there was a statistically significant difference in serum uric acid levels (p=0.0001) in male patients when compared to females. This is in concordance with the study by Tuomilheto et al[78] in which there was no significant association between serum uric acid level and diabetic levels.

Dyslipidemia was present in 71 % of the individuals and it was absent in 29% of the individuals. There was no significant difference in serum uric acid levels as regards to the presence and absence of dyslipidemia.

The mean serum uric acid levels were compared among the three common causes of heart failure encountered in the study that is CAD, RHD and COPD/cor pulmonale . It was found that the p value was > 0.9999 and it was not significant using the ANOVA test.

Among the 100 patients 19 were in class II HF, 76 patients were in class III HF and 5 were in class IV HF. The serum uric acid among the three

groups was compared using ANOVA test and was found to be statistically significant $p<0.05$. Patients in class IV HF had higher uric acid levels than those on class III and class II HF. Hence we observed that as the class of HF worsened there was an increase in uric acid as well.

The mean serum uric acid levels of the patients were compared before and after treatment of HF and it was found that $p >0.05$, not significant. Hence we inferred that probably uric acid is not just a marker but it has a causative role as well. However due to the presence of co-morbid illnesses which also influence the uric acid levels, this could not be hypothesised.

The observations that we have made suggests a role for primary prevention of heart failure. But the literature is conflicting on whether a reduction in serum uric acid will result in measurable clinical benefit among those with established heart failure.[42,43] Some studies have even shown that that increased serum uric acid caused by diuretic use might have a beneficial role in itself.[43] On the other hand, the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study has found that the uricosuric property of Losartan, has a beneficial effect among patients with hypertension and left ventricular remodelling and hypertrophy.[44] The mechanisms by which uric acid reduction treatments is beneficial is not clear. Specifically, it is unclear whether the observed benefit from the use of xanthine oxidase inhibitors is mediated

through reduction in serum uric acid levels or some other mechanism. Inhibition of xanthine oxidase enzyme by allopurinol has beneficial effects in terms of improved peripheral vasodilator capacity, systemic blood flow, and clinical outcomes.[45,46] Randomized controlled studies are also unclear about the potential benefits of allopurinol or its metabolite oxypurinol on heart failure. The La Plata study showed an improvement in left ventricular ejection fraction with the use of allopurinol[47] but the Oxypurinol Therapy for Congestive Heart Failure (OPT-CHF) study did not show an overall benefit.[48]

At the end of 30 days' follow up, 13 Patients expired in our study. 2 of them had normal uric acid levels. Out of the 11 patients who had higher uric acid levels, 5 were in class IV heart failure and 6 were in class III heart failure. Their mean uric acid was found to be 8.9 mg/dl with a minimum of 7.1 mg/dl and a maximum of 12 mg/dl. The relative risk of all cause mortality in those with uric acid > 7.0 mg/dl was found to be 5.72 as compared to 0.1745 for those with uric acid < 7.0mg/dl . The significance of difference in serum uric acid between those who were alive and those who expired was made out using unpaired t test and was found to be extremely significant $p<0.001$. This is in concordance with other studies as shown in the table below:

SOURCE	NO.	EF %	FOLLOW UP mth	SUA in mg/dl	DEATH %
Pascual-Figal et al[9] (2007)	212	31±8	20.4	<5.8 5.8–7.2 7.2–9.1	3. 4 17 60
Jankowska et al[15] (2007)	119	32±8	48.3	<6.5 >6.5	11 29
Sakai et al[16] (2006)	148	35±1	42	<6 >6	8 26
Anker et al[10] (2003)	294	26±15	51	<6.7 6.7-10 10.1-13.4 >13.4	27 40 82 100
Alimonda et al[11] (2009)	560	NR	12	<7.7 >7.7	21 38
Niizeki et al[8] (2006)	123	40±18	38	<5 5.1-6.4 6.5-8.6 >8.6	10 22 30 60

In summary, our study found that hyperuricemia is associated with greater incidence of heart failure and hyperuricemia is a predictor of all cause mortality in patients with heart failure. Future studies using various urate reduction treatment strategies would be needed to determine whether primary prevention of heart failure is possible. As the prevalence of heart failure is increasing , even a small clinical benefit derived from such studies can be of enormous benefit to the community.

Our study had certain limitations. Our sample size was only 100. Moreover, patients were followed for only 30 days and increasing the duration of follow up to at least 6 months or one year would have provided a better assessment of differences in mortality between the two groups.

CONCLUSION

- Serum uric acid levels are higher in patients of heart failure as compared to normal age and sex matched healthy persons.

- Patients in higher NYHA Class of heart failure have higher serum uric acid levels, thus serum uric acid levels correlated with NYHA Class of heart failure.

- Uric acid is not only a bystander marker but probably also a causative marker of mortality in patients who have heart failure.

- Combination of NYHA Class of heart failure and serum uric acid level is a good predictor of mortality of heart failure.

- Any drug interventions, such as therapy to decrease serum uric acid in addition to other drugs used in heart failure, may have a favourable outcome in patients who have heart failure. Further prospective studies are needed to clarify this aspect.

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PROFORMA

Name: Age: Sex:

Address: Occupation:

Duration and details of cardiac illness:

Symptoms:

- ☐ Dyspnea
- ☐ Orthopnea
- ☐ PND
- ☐ Oliguria
- ☐ Abdominal distension
- ☐ Swelling of legs
- ☐ Nocturia
- ☐ Puffiness of Face
- ☐ Chest pain
- ☐ Anorexia
- ☐ Easy fatiguability

Past history:

- ☐ DM
- ☐ Hypertension
- ☐ Tuberculosis

Drug history:

Personal history:

- ☐ Smoking
- ☐ Alcoholism

General examination:

Anthropometry:

Ht: Wt:

Hydration Status: JVP:

Pulse: Blood pressure:

Systemic examination:

CVS: RS: ABDOMEN: CNS:

NYHA class of heart failure:

Investigations:

Hb: TC: DC: P- L- E- M- Plt: ESR:

Blood Glucose Fasting :

Blood Urea :

Serum Creatinine :

Serum Electrolytes : Na+ K+

Total Cholesterol : HDL :

Triglycerides : LDL :

Liver function test :

Bilirubin Total :
Direct :

SGOT :

SGPT :

Total Protein :
Albumin :

Globulin :
Sr. Alkaline Phosphatase :

Urine examination:

ECG:

X-ray chest pa view :

Echocardiogram :

Serum uric acid on admission : Treatment given:

Serum uric acid after treatment :

MASTER CHART FOR PATIENTS

NO.	NAME	AGE	SEX	SYMPTOMS					CAUSE OF HF									DURATION IN MONTHS	DM	SHT	SMOKING	ALCOHOL	EF	NYHA CLASS	DYSLIPIDEMIA	U.A mg/dl DAY1	U.A AFTER TREATMENT	MORTALITY
				DYSPNEA	ORTHOPNEA	ABDOMEN DISTENSION	PEDAL EDEMA	OLIGURIA	CAD	RHD	COPD/COR PULMONALE	CALCIFIC AS/AR	EISENMENGER SYN.	DCM-CAUSE UNKNOWN	ALCOHOLIC C.MYOPATHY	RVD	PERIPARTUM											
1	GANESAN	55	M	P	P	A	P	A	P	A	A	A	A	A	A	A	A	12	P	P	P	P	45	III	P	8.6	8.3	A
2	RAJENDIRAN	52	M	A	A	A	A	A	P	A	A	A	A	A	A	A	A	9	A	P	P	A	48	II	A	4.2	3.9	A
3	LAKSHMI	60	F	P	P	P	P	P	P	A	A	A	A	A	A	A	A	18	P	P	A	A	40	III	P	4.5	4.1	P
4	ANBU	50	M	P	P	P	P	P	A	A	P	A	A	A	A	A	A	6	A	A	P	P	55	II	A	9.9	9.9	P
5	KUPPUSAMY	65	M	P	P	A	P	A	A	A	A	P	A	A	A	A	A	24	A	A	A	P	50	III	P	8.2	7.4	A
6	KANNAGI	55	F	A	A	A	A	A	P	A	A	A	A	A	A	A	A	24	A	A	A	A	48	II	A	1.8	1.6	A
7	JOTHI	50	F	A	A	A	A	A	P	A	A	A	A	A	A	A	A	12	A	A	A	A	48	II	A	2.4	2.3	A
8	LALITHA	62	F	A	A	A	A	A	A	A	A	P	A	A	A	A	A	8	A	A	A	A	49	II	A	3.2	2.9	A
9	ANNAMALAI	55	M	P	A	A	P	A	P	A	A	A	A	A	A	A	A	6	A	P	A	P	42	III	A	7.4	7.1	A
10	DHANAPAL	59	M	P	A	A	P	A	P	A	A	A	A	A	A	A	A	15	A	P	P	P	45	III	A	7.3	6.9	A
11	MURUGAN	46	M	P	P	P	P	P	A	A	A	A	A	P	A	A	A	15	A	A	A	A	35	IV	P	11	12	P
12	KATHIRVEL	45	M	P	A	A	A	A	P	A	A	A	A	A	A	A	A	14	P	P	P	P	50	III	A	4.9	4.6	P
13	VIMALA	40	F	P	P	P	P	P	A	A	A	A	A	P	A	A	A	12	A	A	A	A	34	III	A	7.2	6.8	A
14	ARUMUGAM	42	M	P	P	P	P	P	A	A	A	A	A	A	A	P	A	8	A	A	P	P	40	III	A	6.9	6.6	A
15	KANCHANA	55	F	P	A	A	P	A	P	A	A	A	A	A	A	A	A	6	P	P	A	A	48	III	P	5.8	5.3	A
16	PERIYASAMY	32	M	P	A	A	A	A	P	A	A	A	A	A	A	A	A	8	A	P	A	A	45	III	A	7.9	6.6	A
17	SRINIVASAN	40	M	A	A	A	A	A	P	A	A	A	A	A	A	A	A	12	A	A	P	A	45	III	A	6	5.5	A
18	RANI	45	F	P	P	P	P	P	A	P	A	A	A	A	A	A	A	24	A	A	A	A	48	III	A	5.4	5.1	A
19	LEELAVATHY	28	F	P	P	A	P	A	A	A	A	A	A	A	A	A	P	1	A	A	A	A	45	III	A	4.8	4.2	A
20	SHANMUGAM	62	M	P	P	P	P	P	A	A	P	A	A	A	A	A	A	9	A	A	P	P	56	IV	P	7.4	7.2	P
21	VIJAYAKUMAR	45	M	P	P	P	P	P	A	A	A	A	P	A	A	A	A	18	A	A	P	P	48	III	P	6.9	7.1	P
22	BHARANIVELAN	40	M	P	A	A	P	A	P	A	A	A	A	A	A	A	A	24	P	A	A	A	48	III	P	10	9.9	P

MASTER CHART FOR PATIENTS

NO.	NAME	AGE	SEX	SYMPTOMS					CAUSE OF HF																	
				DYSPNEA	ORTHOPNEA	ABDOMEN DISTENSION	PEDAL EDEMA	OLIGURIA	CAD	RHD	COPD/COR PULMONALE	CALCIFIC AS/AR	EISENMENGER SYN.	DCM-CAUSE UNKNOWN	ALCOHOLIC C.MYOPATHY	RVD	PERIPARTUM	DURATION IN MONTHS	DM	SHT	SMOKING	ALCOHOL	EF	NYHA CLASS	DYSLIPIDEMIA	U.A mg/dl DAY1	U.A AFTER TREATMENT	MORTALITY
23	LOGAMMAL	65	F	P	A	A	P	A	P	A	A	A	A	A	A	A	A	15	P	P	A	A	51	III	P	6.2	6.1	A
24	DEVAKI	50	F	A	A	A	A	A	A	P	A	A	A	A	A	A	A	18	A	A	A	A	60	II	A	3.4	2.6	A
25	PARAMASIVAM	62	M	P	A	A	A	P	A	A	P	A	A	A	A	A	A	13	P	A	P	A	58	III	A	7.4	7.3	A
26	KRISHNAMMAL	58	F	P	A	A	P	A	P	A	A	A	A	A	A	A	A	24	A	P	A	A	48	III	A	5.4	5.1	A
27	VELAYUDHAM	60	M	P	P	P	A	P	A	A	P	A	A	A	A	A	A	24	A	A	P	P	55	III	A	5.9	5.4	A
28	SULOCHANA	59	F	P	P	A	A	P	P	A	A	A	A	A	A	A	A	15	P	A	A	A	45	III	A	6.5	6.4	A
29	MANNANGATTI	62	M	A	A	A	A	A	P	A	A	A	A	A	A	A	A	14	P	P	P	P	48	II	A	4.9	4.7	A
30	SUSEELA	65	F	A	A	A	A	A	P	A	A	A	A	A	A	A	A	13	P	P	A	A	40	II	A	1.2	1.2	A
31	JEYASEELAN	35	M	P	P	P	P	P	A	A	A	A	A	A	P	A	A	8	A	A	A	P	35	III	A	8.2	8.1	P
32	PADMANABAN	60	M	P	A	A	A	A	P	A	A	A	A	A	A	A	A	12	P	P	P	P	48	II	A	7.4	7.1	A
33	RENUKA	28	F	P	A	A	P	A	A	A	A	A	A	A	A	A	P	1	A	A	A	A	49	III	A	3.4	3.2	A
34	SIVAGAMI	50	F	P	P	A	P	P	P	A	A	A	A	A	A	A	A	18	P	P	A	A	35	III	P	6.9	6.7	A
35	LATHA	51	F	P	P	P	P	P	A	P	A	A	A	A	A	A	A	36	A	A	A	A	52	III	A	4.9	4.6	A
36	NAGOORAN	50	M	P	A	A	P	A	A	P	A	A	A	A	A	A	A	18	A	A	P	A	62	III	A	4.2	4	A
37	DAVID	60	M	P	P	P	P	P	A	A	P	A	A	A	A	A	A	24	P	A	P	A	58	III	P	8.2	8.1	P
38	KUYILAMMAL	65	F	P	P	A	P	A	P	A	A	A	A	A	A	A	A	18	P	A	A	A	37	III	P	3.2	3.1	A
39	EGAMBARAM	58	M	P	P	P	P	P	P	A	A	A	A	A	A	A	A	16	A	A	P	P	26	III	A	8.1	7.9	A
40	RAVAKANNU	62	M	P	P	A	P	A	A	P	A	A	A	A	A	A	A	18	A	A	P	A	50	III	A	6.9	6.4	A
41	KARPAGAMMAL	55	F	P	P	A	P	A	P	A	A	A	A	A	A	A	A	13	A	A	A	A	42	III	A	6.7	6.1	A
42	LOGHU	42	M	P	P	P	P	P	A	A	A	A	A	A	P	A	A	5	A	A	P	P	28	IV	P	11.3	11.1	P
43	VIJAYA	58	F	P	A	A	A	A	P	A	A	A	A	A	A	A	A	18	P	A	A	A	35	III	P	5.6	5.1	A
44	MAGENDRAN	50	M	P	A	A	P	A	P	A	A	A	A	A	A	A	A	24	P	P	P	P	29	III	A	8.4	8.5	P

MASTER CHART FOR PATIENTS

NO.	NAME	AGE	SEX	SYMPTOMS					CAUSE OF HF									DURATION IN MONTHS	DM	SHT	SMOKING	ALCOHOL	EF	NYHA CLASS	DYSLIPIDEMIA	U.A mg/dl DAY1	U.A AFTER TREATMENT	MORTALITY
				DYSPNEA	ORTHOPNEA	ABDOMEN DISTENSION	PEDAL EDEMA	OLIGURIA	CAD	RHD	COPD/COR PULMONALE	CALCIFIC AS/AR	EISENMENGER SYN.	DCM-CAUSE UNKNOWN	ALCOHOLIC C.MYOPATHY	RVD	PERIPARTUM											
45	RAMACHANDRAN	69	M	P	P	P	P	P	A	A	P	A	A	A	A	A	A	18	A	A	P	P	58	III	A	6.7	6.2	A
46	RAJESHWARI	42	F	P	P	A	A	A	A	A	A	A	P	A	A	A	A	3	A	A	A	A	58	III	A	4.5	4.2	A
47	PONNURANGAN	48	M	A	A	A	A	A	A	P	A	A	A	A	A	A	A	12	P	P	P	P	45	II	A	4.1	3.9	A
48	ARUMUGAM	49	M	P	P	A	A	A	A	P	A	A	A	A	A	A	A	13	A	A	A	A	48	III	A	6.4	6.1	A
49	PARAMESHWARI	49	F	P	P	A	A	P	A	P	A	A	A	A	A	A	A	18	A	A	A	A	52	III	P	1.8	1.6	A
50	ARJUNAN	42	M	P	P	P	P	A	A	A	A	A	A	A	A	P	A	3	A	A	A	A	42	III	P	8.7	8.2	A
51	SHANTHI	55	F	P	P	A	A	A	P	A	A	A	A	A	A	A	A	6	P	P	A	A	48	III	A	5.8	5.4	A
52	BUVANA	62	F	P	P	A	A	A	P	A	A	A	A	A	A	A	A	12	P	P	A	A	35	III	A	4.9	4.2	A
53	SEKAR	68	M	P	P	A	P	A	A	P	A	A	A	A	A	A	A	24	A	A	P	P	58	III	P	7.9	7.3	A
54	MOHAN	35	M	P	P	P	P	P	A	A	P	A	A	A	A	A	A	8	A	A	P	A	42	III	A	7.9	7.6	A
55	VETRIVEL	45	M	P	P	P	P	P	A	A	A	A	A	P	A	A	A	4	A	A	P	A	35	III	A	8.4	8.3	A
56	SANGEETHA	32	F	P	A	P	A	A	A	P	A	A	A	A	A	A	A	24	A	A	A	A	48	III	A	5.6	5.4	A
57	SUNDARAM	49	M	P	A	A	A	A	A	P	A	A	A	A	A	A	A	12	P	P	P	P	42	III	A	3.4	4.2	A
58	MOHD. BEGUM	52	F	P	A	A	A	P	A	A	P	A	A	A	A	A	A	24	A	A	A	A	48	III	A	3.8	3.9	A
59	MOHD. IQBAL	49	M	A	A	A	A	A	P	A	A	A	A	A	A	A	A	24	P	P	P	A	49	II	A	7.9	6.1	A
60	KANNIYAPPAN	52	M	A	A	A	A	A	P	A	A	A	A	A	A	A	A	12	P	P	P	P	39	II	A	8.2	7.9	A
61	SENTHIL KUMAR	53	M	P	P	A	P	A	P	A	A	A	A	A	A	A	A	12	P	P	P	P	44	III	A	8.2	7.4	A
62	PALANIAPPAN	50	M	A	A	A	A	A	P	A	A	A	A	A	A	A	A	9	A	P	P	A	47	II	P	5.6	5.3	A
63	BANUMATHY	61	F	P	P	P	P	P	P	A	A	A	A	A	A	A	A	18	P	P	A	A	39	III	A	6.4	6.3	A
64	KONDAIAH	49	M	P	P	P	P	P	A	A	P	A	A	A	A	A	A	6	A	A	P	P	54	III	A	8.4	7.9	A
65	KASINATHAN	64	M	P	P	A	P	A	A	A	A	P	A	A	A	A	A	24	A	A	A	A	49	III	A	8.2	7.2	A
66	MANJULA	54	F	A	A	A	A	A	P	A	A	A	A	A	A	A	A	24	A	A	A	A	47	II	P	5.6	5.4	A

MASTER CHART FOR PATIENTS

NO.	NAME	AGE	SEX	SYMPTOMS					CAUSE OF HF																	
				DYSPNEA	ORTHOPNEA	ABDOMEN DISTENSION	PEDAL EDEMA	OLIGURIA	CAD	RHD	COPD/COR PULMONALE	CALCIFIC AS/AR	EISENMENGER SYN.	DCM-CAUSE UNKNOWN	ALCOHOLIC C.MYOPATHY	RVD	PERIPARTUM	DURATION IN MONTHS	DM	SHT	SMOKING	ALCOHOL	EF	NYHA CLASS	DYSLIPIDEMIA	U.A mg/dl DAY1	U.A AFTER TREATMENT	MORTALITY
67	DEVI	49	F	A	P	A	P	A	A	P	A	A	A	A	A	A	A	12	A	A	A	A	57	II	P	4.8	4.7	A
68	PARIMALA	61	F	A	A	A	A	A	A	A	A	P	A	A	A	A	A	8	A	P	A	A	48	II	P	4.7	4.6	A
69	DEVANATHAN	54	M	P	A	A	P	A	P	A	A	A	A	A	A	A	A	6	A	P	P	P	41	III	A	9.8	9.6	A
70	BAALAIAH	58	M	P	A	A	P	A	P	A	A	A	A	A	A	A	A	24	A	A	A	A	34	III	A	6.4	6.1	A
71	MURUGESAN	45	M	P	P	P	P	P	A	A	A	A	A	P	A	A	A	15	P	P	P	P	49	IV	A	9.8	9.6	P
72	SAKTHIVEL	44	M	P	A	A	A	A	P	A	A	A	A	A	A	A	A	14	A	A	A	A	33	III	A	4.9	4.6	A
73	VANAJAMMAL	39	F	P	P	P	P	P	A	A	A	A	A	P	A	A	A	12	A	A	A	A	39	III	A	6.4	6.1	A
74	PANDIYAN	42	M	P	P	P	P	P	A	A	A	A	A	A	A	P	A	8	P	P	A	A	47	III	P	8.8	8.2	A
75	KALAIYARASI	54	F	P	A	A	P	A	P	A	A	A	A	A	A	A	A	6	A	P	A	A	44	III	P	5.8	5.6	A
76	SAMIKANNU	31	M	P	A	A	A	A	P	A	A	A	A	A	A	A	A	24	A	A	P	A	44	III	A	8.9	8.6	A
77	VASAN	39	M	A	A	A	A	A	P	A	A	A	A	A	A	A	A	15	A	A	A	A	47	III	A	6	5.5	A
78	RATHI	44	F	P	P	P	P	P	A	P	A	A	A	A	A	A	A	14	A	A	A	A	44	III	A	6.1	5.9	A
79	SORNA	27	F	P	P	A	P	A	A	A	A	A	A	A	A	A	P	12	A	A	A	A	55	III	A	4.8	4.2	A
80	GOVINDAN	61	M	P	P	P	P	P	A	A	P	A	A	A	A	A	A	8	A	A	P	P	47	III	P	8.9	8.6	A
81	JEYENDRAN	45	M	P	P	P	P	P	A	A	A	A	A	P	A	A	A	14	A	A	A	A	35	IV	P	7.4	7.1	P
82	BALAN	44	M	P	A	A	A	A	P	A	A	A	A	A	A	A	A	12	P	P	P	P	49	III	A	4.8	4.3	A
83	LOGESHWARI	39	F	P	P	P	P	P	A	A	A	A	A	P	A	A	A	11	A	A	A	A	33	III	A	4.2	3.9	A
84	DEVAN	41	M	P	P	P	P	P	A	A	A	A	A	A	A	P	A	9	A	A	P	P	38	III	A	9.1	8.7	A
85	CHINNASAMY	41	M	P	P	P	P	P	P	A	A	A	A	A	A	A	A	4	P	A	P	A	34	III	A	7.4	7.3	A
86	KRISHNAVENI	56	F	P	A	A	P	A	P	A	A	A	A	A	A	A	A	18	P	P	A	A	42	III	A	4.3	4.3	A
87	VIJAYENDRAN	31	M	P	A	A	A	A	P	A	A	A	A	A	A	A	A	7	A	P	A	A	44	III	P	7.9	7.4	A
88	SRIDEVI	44	F	P	A	A	A	A	P	A	A	A	A	A	A	A	A	13	P	P	A	A	49	III	A	4.8	4.6	A

MASTER CHART FOR PATIENTS

NO.	NAME	AGE	SEX	SYMPTOMS					CAUSE OF HF									DURATION IN MONTHS	DM	SHT	SMOKING	ALCOHOL	EF	NYHA CLASS	DYSLIPIDEMIA	U.A mg/dl DAY1	U.A AFTER TREATMENT	MORTALITY
				DYSPNEA	ORTHOPNEA	ABDOMEN DISTENSION	PEDAL EDEMA	OLIGURIA	CAD	RHD	COPD/COR PULMONALE	CALCIFIC AS/AR	EISENMENGER SYN.	DCM-CAUSE UNKNOWN	ALCOHOLIC C.MYOPATHY	RVD	PERIPARTUM											
89	MADURAI	61	M	A	A	A	A	A	P	A	A	A	A	A	A	A	A	13	P	P	P	P	47	II	A	4.9	4.6	A
90	SANGAVI	27	F	P	P	A	P	A	A	A	A	A	A	A	A	A	P	1	A	A	A	A	44	III	A	3.2	2.8	A
91	KUMAR	44	M	P	P	P	P	P	A	A	A	A	A	A	A	P	A	7	A	A	P	P	47	III	P	9.8	9.2	A
92	PALANIVEL	39	M	P	A	A	P	A	P	A	A	A	A	A	A	A	A	24	P	A	A	A	47	III	P	8.9	8.2	A
93	KANNAGI	49	F	A	A	A	A	A	A	P	A	A	A	A	A	A	A	17	A	A	A	A	54	II	A	3.1	2.9	A
94	MUNUSAMY	61	M	P	A	A	A	P	A	A	P	A	A	A	A	A	A	23	A	P	A	A	53	III	A	8.4	8.1	A
95	KRISHNAN	62	M	P	A	A	A	P	A	A	P	A	A	A	A	A	A	18	A	P	A	A	52	III	P	7.4	7.1	A
96	VENI	57	F	P	P	A	A	P	P	A	A	A	A	A	A	A	A	14	P	A	A	A	44	III	A	6.2	5.9	A
97	PALANI	59	M	A	A	A	A	A	P	A	A	A	A	A	A	A	A	13	P	P	P	P	47	II	A	4.9	4.6	A
98	PRIYA	34	F	P	P	P	P	P	A	A	A	A	A	P	A	A	A	11	A	A	A	A	33	III	A	5.6	5.3	A
99	KAMALAKANNAN	61	M	A	A	A	A	A	P	A	A	A	A	A	A	A	A	12	P	P	P	P	48	II	A	4.9	4.8	A
100	HEMALATHA	40	F	P	P	P	P	P	A	A	A	A	P	A	A	A	A	10	A	A	A	A	62	III	A	7.4	7.3	A

KEY TO MASTER CHART:CAD=Coronary artery disease;RHD=Rheumatic heart disease;COPD=Chronic obstructive pulmonary disease;SYN=Syndrome;AS/AR=Aortic stenosis/aortic regurgitation;DCM=Dilated cardiomyopathy;RVD=Retroviral disease DM=Dibetes mellitus;SHT=Systemic hypertension;EF=Ejection fraction;NYHA=Newyork heart association;U.A=Uric acid; A=Absent;P=Present

MASTER CHART FOR CONTROLS

	NAME	AGE	SEX	S.U.A (mg/dl)
1	RENUGA DEVI	27	F	2.9
2	RAJESWARI	41	F	3.2
3	KUNJAMMAL	68	F	4.2
4	RAJENDRAN	64	M	3.4
5	THAVAMANI	45	F	3.7
6	REJINA	33	F	3.9
7	SANTHA	60	F	3.4
8	LATHA	25	F	3.3
9	PRAKASH	33	M	3.7
10	RAMESH	32	M	3.9
11	JACOB	41	M	3.7
12	NAGARAJ	50	M	3
13	NARAYANASAMY	68	M	3.2
14	VEERAPPAN	62	M	4.5
15	KUSALAVAN	44	M	3.7
16	GOVINDARAJAN	58	M	2.8
17	MURTHY	67	M	3.3
18	VENKATESH	33	M	3.8
19	PRABHU	30	M	2.9
20	PETHARAJ	48	M	3.1
21	SANKARI	28	F	3
22	PRIYA	42	F	3
23	DEVI	26	F	3.2
24	KALA	65	F	3.6
25	RAMA	46	F	3.8
26	UMA	34	F	4
27	MARIAMMAL	66	F	4
28	GEETHA	65	F	4.2
29	BOMMI	34	F	3.8
30	SELVAM	33	M	4
31	SHYAM	42	M	3.8
32	VIGNESH	66	M	3.2
33	KISHORE	52	M	3
34	NIRMAL	44	M	3
35	MANOHAR	58	M	4.6
36	SUBHASH	63	M	4.5
37	GOPU	54	M	4.1
38	SELVAM	67	M	4
39	VISWA	38	M	3.9
40	RAMU	28	M	4.1

KEY:U.A=Uric acid

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No: 04425305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. Vijayshree .G
PG in MD General Medicine
Madras Medical College, Chennai -3.

Dear Dr. Vijayshree .G

The Institutional Ethics Committee of Madras Medical College reviewed and discussed your application for approval of the proposal entitled " Role of serum uric acid as a biomarker in heart failure " No. 19042011.

The following members of Ethics Committee were present in the meeting held on 21.04.2011 conducted at Madras Medical College, Chennai -3.

1.	Prof. S.K. Rajan, MD	-- Chairperson
2.	Prof. V. Kanagasabai MD Dean, Madras Medical College, Chennai-3,	-- Deputy chairman
3.	Prof. A. Sundaram, MD Vice Principal , Madras Medical College, Chennai -3	-- Member Secretary
4.	Prof R. Sathianathan MD	-- Member
5.	Prof R. Nandhini, MD Director, Institute of Pharmacology, MMC, Ch-3	-- Member
6.	Prof. Pregna B. Dolia MD Director , Institute of Biochemistry, MMC, Ch-3	-- Member
7.	Prof. C. Rajendiran .MD Director , Institute of Internal Medicine, MMC, Ch-3	-- Member
8.	Thiru. A. Ulaganathan Administrative Officer, MMC, Chennai -3	-- Layperson
9.	Thiru. S. Govindasamy . BA.BL	-- Lawyer
10.	Tmt. Arnold Soulina	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd /. Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report

Member Secretary, Ethics Committee